Psychoeducational interventions targeting core symptoms to achieve remission and prevent relapses and recurrence in depression.

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The Core of Depression

Contents continued overleaf...

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...Contents continued from cover page

The Core of Depression

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Is the identification of the core symptoms of depression clinically relevant?

by H. J. Möller, Germany

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THIS ISSUE OF *MEDICOGRAPHIA* DEALS WITH THE CORE SYMPtoms of depression, a topic that is not only relevant for the diagnosis and treatment of depression, but also for theories about its etiopathogenesis. This subject can be addressed from different perspectives, as is apparent in the various contributions in this issue. The first group of articles covers a clinical point of view, and each asks whether certain specific symptoms like depressed mood, retardation and anhedonia, sleep disturbances, or sexual disorders belong to the core symptoms of depression. Other articles describe the assessment of core symptoms of depression and discuss the psychometric relevance of specific symptoms for the subtyping of major depressive disorders. Etiopathogenetic factors such as chronobiological and brain imaging aspects are also covered. Finally, the question of how to deal with the core symptoms of depression in primary care, and which core symptoms of depression should be addressed first, are topics of further contributions.

All these are important issues, and different clinical and research approaches have been trying for a long time to clarify them. In the following, I endeavor to show some examples of the issues at hand in order to highlight the relevance of these questions.

It has long been a tradition, on the basis of clinical experience, to distinguish different subtypes of depression and their associated symptom profiles. Melancholic depression, formerly also referred to as endogenous depression, is seen to be the prototype of a "biological" depression and the type most likely to respond positively to antidepressants. This condition has been a topic of discussion for a long time, and was recently addressed by Parker et al[1] on the basis of new research data focusing on the relevance of somatic symptoms, among others. On the basis of results of routine care documentation, Parker and colleagues came to the conclusion that tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were the most effective pharmacological treatments for melancholic depression, while the newer agents (selective serotonin reuptake inhibitors [SSRIs], reversible inhibitors of monoamine oxidase A, and antipsychotic drugs) were much less effective. In a subsequent publication, albeit of preliminary results, Parker found that although TCAs and SSRIs did not differ distinctly in their effectiveness in younger patients with melancholia, SSRIs were less effective in older melancholic patients, and that this effect was unlikely to be secondary to age of disorder onset or to the length of lifetime depressive experience.[2] In the author's view, an understanding of the impact of age on antidepressant drug response across melancholic and nonmelancholic depressive subtypes may help to clarify differential drug effectiveness patterns, and to link the underlying neuropathological changes to clinical management, including choice of antidepressant.

The traditional concept of atypical depression, which has recently gained renewed interest, presents, to a certain degree, quite the opposite situation. In contrast to "typical" depression, major depression, and especially its most representative subtype, melancholic depression, is

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characterized by symptoms such as mood reactivity and increased sleep and appetite.[3] Atypical depression is not as rare as is sometimes believed: a frequency of up to 20% to 30% has been reported in an outpatient setting.[3] Atypical depression does not seem to respond well to classic antidepressants like the TCAs, but to be more sensitive to MAOIs.[4] Most clinical research has been conducted on traditional MAOIs. The newer selective and reversible inhibitors of MAO-A promise lower toxicity and better tolerance and may thus turn out to be a better alternative than the older MAOIs. It has been hypothesized that the serotonin system may be involved in the etiopathogenesis of atypical depression[5]; in this case, SSRIs could be expected to show clinical efficacy in this subtype of depression; however, as yet insufficient data on this question are available.

Other subtypes of depression also seem to be of clinical relevance, for example, psychotic depression, anxious depression, agitated depression, retarded depression, etc. All these subtypes have implications in terms of drug treatment, for example, combination of an antidepressant and a neuroleptic in psychotic depression, or of an antidepressant and a benzodiazepine in anxious depression.

Besides their relevance to clinical decision-making, these subtypes may also be of interest in neurobiological research. Although no clear associations between these different features and any particular neurobiological parameter have been found to date, it can be expected that the development of more sophisticated methods like molecular genetics will increase the chance of discovering such links.

Bipolar depression is also relevant in this context. Differential diagnosis is primarily based on aspects of the disease course (manic/hypomanic episodes). However, some experts emphasize that there might also be some differences in the cross-sectional pattern of clinical symptoms. This view seems primarily to stem from the existence of mixed states, during which patients experience both depressive and (some) manic symptoms.

Besides these clinically based differentiations and subtypes, the field of psychopathometrics developed as another line of research to try to differentiate between core and secondary/associated symptoms. Factor analyses and other multivariate approaches were applied to data obtained from measurements with depression scales in cross-sectional and longitudinal studies in an attempt to define subdimensions of depressive symptomatology like the Hamilton Depression Scale (HAMD) subscores for "depressive inhibition," "depressive agitation," "anxiety," and "somatic symptoms." The question of depressive core symptoms was also addressed in this context[6,7] as well as their relevance for response to treatment with antidepressants.[7-9] Bech et al first defined the melancholia subscale (now referred to as the "HAMD depression factor") of the HAMD using a probabilistic test model. They found that the original 17-item HAMD was without adequate consistency as a measure of the severity of depressive states and that a subscale consisting of the 6 items depressed mood, guilt, work and interests, retardation, psychotic anxiety, and general somatic symptoms delivered more reliable results.[10] In later meta-analyses, Bech and colleagues showed that the 6-item depression factor was more sensitive to detecting antidepressive effects of fluoxetine[7] and mirtazepine[9] than the total 17-item HAMD. Similar results were obtained by using another statistical approach, the facet theory in combination with nonmetric multidimensional scaling procedures.[6] In an evaluation of two sertraline-amitriptyline studies,[11,12] it was found that the efficacy of TCAs was no longer superior to that of the SSRIs when only the core symptoms of depression were considered instead of the full HAMD scale.[8] The total score of the HAMD seems to have an inherent bias toward more sedative antidepressants, but this bias can be avoided by considering the depression factor, while the additional items of the HAMD-17 can be used to describe other characteristics of the depressive symptomatology.

In recent years, extensive research has been performed to evaluate how best to screen for and diagnose depression in primary care.[13,14] The results indicate that symptoms that are traditionally not seen as being core or "specific" symptoms, but that occur very frequently in depression, such as reduced well-being or sleep problems, can be used very effectively for screening purposes. This underlines the importance of sleep disturbances—which are not only very common symptoms in primary care patients, but also one of the most frequent symptoms of depression—as a potential indicator of depression.[15-18] The fact that "sleep disturbances" not only belong to the most frequently reported symptoms in depression, but also show some specificity in polysomnographic sleep pattern analysis,[19] indicates that these sleep disturbances might have special neurobiological relevance in the context of depression.

This brings us to the intriguing subject of psychopharmacological interventions that focus primarily on symptoms such as sleep disorders,[20] which are not always regarded as core symptoms. It was recently demonstrated using a sophisticated statistical analysis that excluded potential confounders, that beyond the positive effects on sleep, treatment of depressive patients with a hypnotic could also reduce the severity of depression.[21] In this context, it is interesting to speculate that the capacity of agomelatine to normalize the disturbed sleep pattern of depressive patients might also contribute to its overall antidepressant efficacy.[22-25] This allows us to hypothesize that not only the classic core symptoms are of relevance for diagnosis and triggering of depression, but also the very frequent and so-called unspecific symptoms like reduced well-being, sadness, and, over all, sleep disorders. These symptoms are possibly more specific in terms of neurobiological mechanisms of depression than is commonly believed on the basis of psychopathological considerations, and this issue of *Medicographia* looks into the debate surrounding their eligibility as "new core syndromes" of depression. ❐

Signature

REFERENCES

1. Parker G. Classifying depression: should paradigms lost be regained? *Am J Psychiatry.* 2000;157:1195-1203.
2. Parker G. Differential effectiveness of newer and older antidepressants appears mediated by an age effect on the phenotypic expression of depression. *Acta Psychiatr Scand.* 2002;106:168-170.
3. Henkel V, Mergl R, Coyne JC, et al. Depression with atypical features in a sample of primary care outpatients: prevalence, specific characteristics and consequences. *J Affect Disord.* 2004;83:237-242.
4. Henkel V, Mergl R, Allgaier AK, Kohnen R, Möller HJ, Hegerl U. Treatment of depression with atypical features: a meta-analytic approach. *Psychiatry Res.* 2006; 141:89-101.
5. Nierenberg AA, Alpert JE, Pava J, et al. Course and treatment of atypical depression. *J Clin Psychiatry.* 1998;59(suppl):18:5-9.
6. Steinmeyer EM, Möller HJ. Facet theoretic analysis of the Hamilton-D scale. *J Aff Disord.* 1992;25:53-61.
7. Bech P, Cialdella P, Haugh MC, et al. Meta-analysis of randomised controlled trials of fluoxetine vs placebo and tricyclic antidepressants in the short-term treatment of major depression. *Br J Psychiatry.* 2000;176:421-428.
8. Möller HJ. Methodological aspects in the assessment of severity of depression by the Hamilton Depression Scale. *Eur Arch Psychiatry Clin Neurosci.* 2001;251(suppl 2):II13-II20.
9. Bech P. Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. *Int J Neuropsychopharmacol.* 2001;4:337-345.
10. Bech P, Allerup P, Gram LF, et al. The Hamilton depression scale. Evaluation of objectivity using logistic models. *Acta Psychiatr Scand.* 1981;63:290-299.
11. Möller HJ, Glaser K, Leverkus F, Göbel C. Double-blind, multicenter comparative study of sertraline versus amitriptyline in outpatients with major depression. *Pharmacopsychiatry.* 2000;33:206-212.
12. Möller HJ, Gallinat J, Hegerl U, et al. Double-blind, multicenter comparative study of sertraline and amitriptyline in hospitalized patients with major depression. *Pharmacopsychiatry.* 1998;31:170-177.
13. Henkel V, Mergl R, Kohnen R, Maier W, Möller HJ, Hegerl U. Identifying depression in primary care: a comparison of different methods in a prospective cohort study. *BMJ.* 2003;326:200-201.
14. Henkel V, Mergl R, Coyne JC, et al. Screening for depression in primary care: will one or two items suffice? *Eur Arch Psychiatry Clin Neurosci.* 2004;254:215-223.
15. Nowell PD, Buysse DJ. Treatment of insomnia in patients with mood disorders. *Depress Anxiety.* 2001;14:7-18.
16. Perlis ML, Giles DE, Buysse DJ, et al. Which depressive symptoms are related to which sleep electroencephalographic variables? *Biol Psychiatry.* 1997;42:904-913.
17. McCall WV, Reboussin BA, Cohen W. Subjective measurement of insomnia and quality of life in depressed inpatients. *J Sleep Res.* 2000;9:43-48.
18. Tylee A, Gastpar M, Lepine JP, Mendlewicz J; DEPRES Steering Committee. DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. *Int Clin Psychopharmacol.* 1999;14:139-151.
19. Farina B, Della MG, Grochocinski VJ, et al. Microstructure of sleep in depressed patients according to the cyclic alternating pattern. *J Affect Disord.* 2003;77:227-235.
20. Möller HJ. Treatment of chronic insomnia in Europe. In preparation.
21. Fava M, McCall WV, Krystal A, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry.* 2006;59:1052-1060.
22. Olie JP, Kasper S. Efficacy of agomelatine, a MT_1/MT_2 receptor agonist with $5\text{-}HT_{2C}$ antagonistic properties, in major depressive disorder. *Int J Neuropsychopharmacol.* 2007;10:661-673.
23. Pandi-Perumal SR, Srinivasan V, Cardinali DP, et al. Could agomelatine be the ideal antidepressant? *Expert Rev Neurother.* 2006;6:1595-1608.
24. Kupfer DJ. Depression and associated sleep disturbances: patient benefits with agomelatine. *Eur Neuropsychopharmacol.* 2006;16(suppl 5):S639-S643.
25. Montgomery SA. Major depressive disorders: clinical efficacy and tolerability of agomelatine, a new melatonergic agonist. *Eur Neuropsychopharmacol.* 2006;16(suppl 5):S633-S638.

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L'identification des symptômes majeurs de la dépression est-elle cliniquement pertinente ?

par H. J. Möller, Allemagne

Ce numéro de Medicographia *aborde, sous diverses perspectives, le sujet des symptômes majeurs de la dépression, dont les implications sont importantes non seulement pour le diagnostic et le traitement, mais aussi pour l'étiopathogénie de cette maladie. Un premier groupe d'articles centrés sur les aspects cliniques cherche à déterminer dans quelle mesure certains symptômes spécifiques comme l'humeur dépressive, l'inhibition et l'anhédonie ou les troubles du sommeil et sexuels font partie des symptômes majeurs de la dépression. Viennent ensuite des articles consacrés aux aspects psychométriques qui passent en revue les méthodes d'évaluation de ces symptômes et examinent leur pertinence dans la classification des troubles dépressifs majeurs. D'autres articles évoquent les facteurs étiopathogéniques à la lumière de l'imagerie cérébrale et de la chronobiologie, tandis que le problème de l'identification des symptômes majeurs prioritaires et comment les traiter dans le cadre de la prise en charge primaire de la dépression est débattu par plusieurs auteurs.*

Tous ces aspects sont importants, et différentes approches cliniques et expérimentales ont tenté de les clarifier depuis longtemps. L'exposé qui suit voudrait citer quelques exemples des sujets qui font encore débat afin de bien faire saisir l'importance des considérations soulevées par les articles de ce numéro.

La différenciation de la dépression en plusieurs sous-types et profils symptomatiques associés est une tradition ancienne, fondée sur l'expérience clinique. La dépression mélancolique, appelée aussi autrefois dépression endogène, est considérée comme le prototype de la dépression « biologique », celle qui est la plus susceptible de répondre positivement aux antidépresseurs. Cette pathologie a longtemps fait l'objet de discussions, Parker et al.[1] *ont fait le point récemment sur de nouvelles données de recherche portant en particulier sur l'importance des symptômes somatiques. Se basant sur les données publiées concernant les traitements habituels, ces auteurs conclurent à la plus grande efficacité des antidépresseurs tricycliques (ATC) et des inhibiteurs de la monoamine oxydase (IMAO) dans la dépression mélancolique, alors que les médicaments plus récents tels les inhibiteurs sélectifs de la recapture de la sérotonine [ISRS], les inhibiteurs réversibles de la monoamine oxydase A, et les antipsychotiques étaient beaucoup moins efficaces. Parker, dans une publication ultérieure, ne concernant cependant que des résultats préliminaires, constate qu'alors que l'efficacité des ATC et des ISRS diffère peu chez les patients mélancoliques les plus jeunes, les ISRS sont moins efficaces chez les patients plus âgés, et il est improbable que cet effet soit secondaire à la date d'installation des troubles ou à la durée de la maladie dépressive[2]. À mon avis, la compréhension de l'influence de l'âge sur la réponse des sous-types de dépression mélancolique ou non mélancolique aux antidépresseurs pourrait éclaircir les différences dans l'efficacité thérapeutique, et permettre de relier les diverses modifications neuropathologiques sous-jacentes à des modalités distinctes de prise en charge clinique, y compris jusque dans le choix de l'antidépresseur.*

Quant au concept traditionnel de dépression atypique, qui a connu récemment un regain d'intérêt, celui-ci se trouve, dans une certaine mesure, dans la situation opposée. Contrairement à la dépression « typique », la dépression majeure, et en particulier son sous-type le plus repré-

sentatif, la dépression mélancolique, se caractérise par des symptômes à type d'humeur réactive et d'augmentation du sommeil et de l'appétit[3]. La dépression atypique n'est pas aussi rare que l'on pense : sa fréquence a été estimée entre 20 % et 30 % en ambulatoire[3]. La dépression atypique ne semble pas bien répondre aux antidépresseurs classiques comme les ATC, mais elle est plus sensible aux IMAO[4]. Les IMAO traditionnels ont fait l'objet de la plupart des études cliniques. Il semble que les inhibiteurs sélectifs et réversibles de la MAO-A les plus récents aient une toxicité plus faible et une meilleure tolérance et qu'ils puissent donc représenter une meilleure alternative que les anciens IMAO. Le système de la sérotonine pourrait être impliqué dans l'étiopathogénie de la dépression atypique[5] avec, pour corollaire, une efficacité clinique des ISRS dans ce sous-type de dépression ; cependant, nous ne disposons pas encore de données suffisantes sur cette question.

D'autres sous-types de dépression semblent cliniquement importants, par exemple la dépression psychotique, la dépression anxieuse, la dépression agitée, la dépression inhibée, etc. Tous ces sous-types ont des incidences en termes de traitement, par exemple, l'association d'un antidépresseur et d'un neuroleptique dans la dépression psychotique, ou d'un antidépresseur et d'une benzodiazépine dans la dépression anxieuse.

Ces sous-types peuvent aussi, en plus de leur importance face à la prise de décision clinique, être intéressants pour la recherche neurobiologique. Bien que de nos jours aucune association claire n'ait été retrouvée entre ces différentes caractéristiques et un paramètre neurobiologique particulier, le développement de méthodes plus sophistiquées comme la génétique moléculaire pourra peut-être accroître la chance de découvrir de tels liens.

La dépression bipolaire rentre aussi dans ce cadre. Le diagnostic différentiel est principalement fondé sur l'évolution de la maladie (épisodes maniaque/hypomaniaque). Certains experts soulignent cependant qu'il peut aussi y avoir des différences transversales du profil symptomatologique clinique. Cette hypothèse semble principalement provenir de l'existence de stades mixtes, au cours desquels les patients présentent à la fois des symptômes dépressifs et (quelques) symptômes maniaques.

À côté de ces différenciations et sous-types fondés sur la clinique, le domaine de la psychopathométrie s'est développé comme une autre ligne de recherche pour essayer d'établir une distinction entre symptômes majeurs et symptômes associés/secondaires. Au cours d'études longitudinales et transversales, des analyses factorielles et d'autres approches multivariées ont été appliquées aux données obtenues à partir des mesures faites avec des échelles de dépression afin de caractériser des sous-catégories de symptomatologie dépressive. C'est ainsi qu'on a pu définir, à partir de l'échelle de dépression de Hamilton (HAMD) des sous-scores pour « l'inhibition dépressive », « l'agitation dépressive », « l'anxiété » et « les symptômes somatiques ». La question des symptômes dépressifs majeurs[6,7] ainsi que de leur importance dans la réponse aux antidépresseurs[7-9] a également été étudiée sous l'angle de la psychopathométrie. Bech et al. *ont commencé par définir une sous-échelle de mélancolie de la HAMD (maintenant appelée «indice de dépression de la HAMD ») au moyen d'un modèle de test de probabilité. Ils ont pu établir que l'échelle originale de la HAMD à 17 items ne convenait pas comme mesure de la sévérité dépressive et qu'une sous-échelle à 6 items (humeur dépressive ; culpabilité ; travail et centres d'intérêt ; inhibition ; anxiété psychotique ; symptômes somatiques généraux) donnait des résultats plus fiables[10]. Dans des métaanalyses ultérieures, Bech* et al. *démontrèrent que l'indice de dépression à 6 items était plus sensible pour déceler les effets antidépresseurs de la fluoxétine[7] et de la mirtazapine[9] que l'échelle HAMD complète à 17 items. Des résultats similaires ont été obtenus par une autre approche statistique associant la théorie des facettes à l'utilisation d'échelles multidimensionnelles non métriques[6]. L'évaluation de deux études comparant la sertraline et l'amitriptyline[11,12] a montré que l'efficacité des ATC ne dépassait pas celle des ISRS lorsque seulement les symptômes majeurs de la dépression étaient pris en compte au lieu de l'échelle complète de l'HAMD[8]. L'utilisation du score total de l'HAMD semble introduire un biais en faveur des antidépresseurs plus sédatifs, mais ce biais peut être évité en prenant en compte l'indice de dépression, les items supplémentaires de l'HAMD-17 pouvant être utilisés pour décrire d'autres caractéristiques de la symptomatologie dépressive.*

Ces dernières années, une recherche approfondie a permis de déterminer les meilleures méthodes de dépistage et de diagnostic de la dépression dans le contexte de la médecine de soins primaires[13,14]. Il a pu être montré que les symptômes qui ne sont pas habituellement considérés comme des symptômes majeurs ou « spécifiques », mais qui surviennent de façon très fré-

quente dans la dépression, comme la diminution du bien-être ou les troubles du sommeil, sont des indicateurs très efficaces pour le dépistage. Ceci souligne l'importance des troubles du sommeil en tant qu'indicateur potentiel de dépression, ceux-ci n'étant pas seulement courants chez les patients de soins primaires, mais aussi une des manifestations les plus fréquentes de la dépression[15-18]*. Le fait que les « troubles du sommeil » comptent non seulement parmi les symptômes les plus fréquemment rapportés dans la dépression, mais se traduisent également par une certaine spécificité dans l'analyse du schéma polysomnographique du sommeil*[19]*, montre que ces troubles peuvent avoir une importance neurobiologique particulière dans le contexte dépressif.*

Ces considérations nous amènent au sujet intéressant des interventions psychopharmacologiques axées en priorité sur des symptômes secondaires tels que les troubles du sommeil[20] *qui ne sont pas toujours considérés comme étant des symptômes majeurs. Une analyse statistique sophistiquée excluant les facteurs confondants potentiels à récemment démontré, au-delà des effets positifs sur le sommeil, que le traitement des sujets déprimés avec un hypnotique pouvait aussi diminuer la sévérité de la dépression*[21]*. Dans ce contexte on peut émettre l'hypothèse que la normalisation des troubles du sommeil sous l'action de l'agomélatine contribue à son efficacité antidepressive globale*[22-25]*. Ceci nous conduit à formuler l'hypothèse que ce ne sont pas seulement les symptômes majeurs classiques qui sont importants pour le déclenchement et le diagnostic de la dépression, mais également les symptômes très fréquents et soit-disant non spécifiques comme la diminution du bien-être, la tristesse et surtout les troubles du sommeil. D'un point de vue psychopathologique, ces symptômes joueraient un rôle plus spécifique qu'on ne le croit communément dans les mécanismes neurobiologiques de la dépression, et ce numéro de* Medicographia *fait le point sur les débats autour de leur acceptabilité en tant que « nouveaux symptômes majeurs » de la dépression.* ❒

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Depressed mood as a core symptom of depression

by P. Bech, Denmark

Sadness or lowered mood is the primary symptom specific to depressive states, as shown by most studies using the Hamilton Depression Rating Scale (HAM-D). In both the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition *and the* International Statistical Classification of Diseases and Health-Related Problems—10th Revision, *"depressed mood" and "loss of interests or pleasure in nearly all activities" are the two "big" symptoms in major depression. The two items overlap in the concept of abulia, which covers both anhedonia and low spirits. The neurovegetative symptoms associated with depressive states should be considered an interactive manifestation of the disease process, but with a less specific symptom rating than depressed mood or anhedonia. Lowered mood should, therefore, not be considered a consequence of the neurovegetative symptoms. Change in lowered mood is the most appropriate indicator of antidepressant effect. Many of the neurovegetative symptoms included in the HAM-D could reflect the side effects of an antidepressant, but the separately evaluated "depressed mood" symptom is a most sensitive indicator of antidepressant effect. This has been confirmed in many placebo-controlled trials. When used as an indicator of global impression of severity, depressed mood shows satisfactory standardization between the various symptom rating scales. Thus were we to go for a HAM-D1 (ie, including only one item and not the half-a-dozen core items in the HAM-D6 within the HAM-D17), this single item should be "depressed mood."*

Medicographia. 2008;30:9-13. *(see French abstract on page 13)*

Keywords: *abulia; acedia; anhedonia; depressed mood; Hamilton Depression Rating Scale; neurovegetative symptom; standardization*

For half a century, depressive illness has been largely quantified using the Hamilton Depression Rating Scale (HAM-D). Factor analysis is the psychometric method most often used when classifying depressive symptoms. Despite the many versions of the HAM-D used (from 17 to 28 symptoms), and the many variants of factor analysis, the results have consistently identified "depressed mood" and "work and interests" as the two "big" symptoms in depressive states. Within the major depression syndrome, according to the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV),*[1] the first two listed symptoms are "depressed mood" and "loss of interest or pleasure in nearly all activities." However, these two core symptoms need to be followed by at least four additional symptoms drawn from a list of seven covering the syndrome of *DSM-IV* major depression.

Depressed mood, or negative affect, and lack of interest, or anhedonia, are components of abulia, a term used by neurologists and neuropsychiatrists to denote lack of spontaneous goal-directed behavior.[2,3] *DSM-IV* describes the essential feature of depressed mood as being sad, hopeless, discouraged, or "down in the dumps." *Table IA (page 10),* which shows the "depressed mood" item in HAM-D, provides a more detailed definition. On revising the HAM-D in 1967, Hamilton observed[4]:

> *Depressed mood is not easy to assess. One looks for a gloomy attitude, pessimism about future, feelings of hopelessness and a tendency to weep… When patients are severely depressed they may "go beyond weeping." It is important to remember that patients interpret the word "depression" in all sorts of strange ways. A useful common phrase is "lowering of spirits." It is generally believed that women weep more readily than men, but there is little evidence that this is true in the case of depressive illness…*

The scoring instructions in *Table IA* were published in 1986, when, with Hamilton's agreement, the HAM-D was revised to cover both men and women.[5]

Unfortunately, many different versions of the HAM-D have been published that were not approved by Hamilton himself. *Table IB (page 10)* shows the

SELECTED ABBREVIATIONS AND ACRONYMS

DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*
GAD	generalized anxiety disorder
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
ICD-10	*International Statistical Classification of Diseases and Health-Related Problems—10th Revision*
IVRS	interactive voice response system
MADRS	Montgomery-Åsberg Depression Rating Scale
MES	Melancholia Scale
PSE	Present State Examination

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HAMILTON DEPRESSION RATING SCALE (HAM-D)

A. "Depressed mood"

0. Not present

1. It is doubtful whether the patient is more despondent or sad than usual; for example, the patient appears vaguely to be more depressed than usual.

2. The patient is more clearly concerned with unpleasant experiences, although he/she still lacks helplessness or hopelessness.

3. The patient shows clear nonverbal signs of depression and/or is at times over-powered by helplessness or hopelessness.

4. The patient's remarks on despondency and helplessness or nonverbal signs dominate the interview.

B. "Depressed mood" (sadness, hopeless, helpless, worthless)

0. Absent

1. These feeling states only indicated on questioning

2. These feeling states spontaneously reported verbally

3. Communicates feeling states nonverbally, ie, through facial expression, posture, voice, tendency to weep

4. Patient reports virtually only these feeling states in his/her spontaneous verbal and nonverbal communication

C. "Work and interests"

0. Not present

1. The patient expresses motivation and/or is carrying out the usual workload. Some feeling of incapacity.

2. The patient shows a more pronounced reduction in motivation and/or has trouble in carrying out daily work activities. Some loss of interest in hobbies; inability to feel affects the family.

3. Difficulties in simple routine activities.

4. Unable to do anything without help.

Table I. Hamilton Depression Rating Scale (HAM-D).

A: Revised to cover men and women, approved by Hamilton.

From: Bech P, Kastrup M, Rafaelsen OJ. Mini-compendium of rating scales for states of anxiety, depression, mania, schizophrenia with corresponding *DSM-III* syndromes. *Acta Psychiatr Scand.* 1986;73(suppl):7-37.[5]

B: A version not approved by Hamilton.

From: Guy W. *Early Clinical Drug Evaluation (ECDEU) Assessment Manual for Psychopharmacology.* Publication No. 76-338. Rockville, MD: National Institute of Mental Health; 1976.[6]

C: "Work and interests" item with definitions updated and approved by Hamilton[4] as an extension of his guidelines.

Abridged and modified from: Bech P. *Rating scales for psychotherapy, health states and quality of life.* Berlin, Germany: Springer; 1993:164-165.[11]

HAM-D version most frequently used in assessing antidepressants in randomized clinical trials of major depression.[6] It elicited the following comment from Hamilton:

> *A further deficiency was that it regarded the spontaneous mention of a symptom as indicating greater severity than if it had been elicited by questioning. There are many reasons why patients may not mention a symptom at an interview. For example, they may not find it relevant (eg, feeling of guilt), they may be embarrassed (eg, loss of libido) or they may be too polite to mention to the interviewer that they believe they are suffering from a physical illness.*[7]

Recently, self-rating versions of the HAM-D have been developed, because such a scale can be considered a structured patient interview. The original Beck Depression Inventory[8] was designed in such a way that a therapy-neutral person had to read the items aloud for the patient. A recent version of such an instrument is the interactive voice response system (IVRS) that has been used for the HAM-D6.[9] *Table II* shows the "depressed mood" item in the HAM-D6 self-rating version.[10]

Table IC shows the HAM-D "work and interests" item. Hamilton's 1967 instructions for an abridged version[11] included the following:

> *It could be argued that the patient's loss of interest in his work and activities should be rated separately from his decreased performance, but it has been found too difficult to do so in practice. Care should be taken not to include fatiguability and lack of energy here; the rating is concerned with loss of efficiency and the extra effort required to do anything.*[4]

Thus "fatigability" and "lack of energy" are not to be included under "work and interests." Patients often say that they no longer care. This is essentially lack of interest, spiritual apathy, or intellectual laziness, sometimes termed "acedia," meaning "absence of caring" in the original Greek (or "sloth," in the context of the seven cardinal sins[12]). The religious historian Clebsch analyzed the first major depressive episode experienced by William James as follows:

> *Acedia is often referred to by "sloth," ie, a general act of laziness. However, acedia is rather an overscrupulous wondering about what one ought to do when faced, as James, by "a kind of experience in which intellect, feeling and will, all our consciousness and all our subconsciousness together melt in a kind of chemical fusion."*[12]

HAMILTON DEPRESSION RATING SCALE (HAM-D): SELF-RATING VERSION (S HAM D6)

"Depressed mood"

0. I have been in my usual good mood

1. I have felt a little more sad than usual

2. I have been clearly more sad than usual, but haven't felt helpless or hopeless

3. I have been so gloomy that I briefly have felt overpowered by hopelessness

4. I have been so low in my moods that everything seems dark and hopeless

Table II. Self-rating version of the Hamilton Depression Rating Scale (HAM-D) scale for "depressed mood."

From: Bech P. Rating scales in depression: limitations and pitfalls. *Dialogues Clin Neurosci.* 2006;8:207-215.[10]

Acedia is closely associated with melancholia, as it prevents the person from doing anything, except perhaps suicide as the only escape from the ennui and guilt of inactivity.[12] Acedia is also very closely associated with abulia. The poet T. S. Eliot, who also suffered recurrent depressive episodes, used the term "aboulie" to describe his own disorder of the will which he found to be the core symptom of depression.[13] He considered depression to be an emotional, not a thinking disorder because it impaired his mood and will, but not his thought processes.

The two "big" core symptoms of depressive illness ("depressed mood" and "work and interests") thus seem to have coalesced by a kind of chemical fusion into abulia or acedia. According to the psychiatrist Storr,[14] William James, T. S. Eliot, and Winston Churchill all experienced abulia in their depressive episodes, but compensated by working hard whenever possible outside their episodes of depression. In their neutral phases recurrent depressives may thus be characterized by enormous vitality and appetite for work.[14]

The *International Statistical Classification of Diseases and Health-Related Problems—10th Revision (ICD-10)*[15] identifies "tiredness" as the third core symptom of depressive illness. A general population study using the Present State Examination (PSE)[16] showed "depressed mood" and "lack of energy" to be among the most common symptoms, while "guilt," "suicide," and "depression worst in the morning" were among the most uncommon *(Table III)*.[17] This study identified the hierarchical pattern of the PSE symptoms in that the rarer the symptom, the higher the total symptom score indicated by its presence. In other words, the prevalence of uncommon symptoms in *Table III* was preceded by a higher prevalence of the most common symptoms.[17]

In several studies using the HAM-D, we have found that six items fulfil this hierarchical pattern in depressed patients.[18] The six items (HAM-D6) are "depressed mood," "work and interests," "general somatic (tiredness and pain)," "anxious mood," "guilt feelings," and "psychomotor retardation" *(Table III)*. This sequence of symptoms reflects their point prevalence in patients with depressive illness.[18] Thus "depressed mood" and "work and interests" have the highest prevalence while "guilt feelings" and "psychomotor retardation" have the lowest prevalence. We used item response theory models (one-parameter Rasch analysis and nonparametric Mokken analysis) to test the hierarchical pattern of these six items. The hierarchical prevalence from "depressed mood" to "psychomotor retardation" *(Table III)* confirms their hierarchical role in the constitution or measurement of depressive states. According to item response theory models, it is precisely because of this difference in the prevalence of the six items, and the fact that persons scoring on the less prevalent items also score on a more prevalent item, that the sum of all six items becomes a valid representation of depression severity.[19]

The separation between "lack of interests" and "lack of energy" in the HAM-D, *DSM-IV* and *ICD-10* is important because "lack of interests" is closer to "depressed mood" than "lack of energy." *Table IV* shows the correlation between the "lack of energy" item and the other items covering depression according to *DSM-IV* and *ICD-10* when reanalyzing the data from the study by Olsen et al.[20] The correlation coefficients are highest for "depressed mood" and "lack of interests" and lowest for "sleep problems," which is consistent with other studies.[21] In the remission phase, after 4 to 6 weeks of therapy, the internal balance between "depressed mood" and "lack of interests" may change. Thus a recurrent depressive might have more work activity than normal between episodes. Such states of overactive neutral mood are now considered hypomanic,[22] and the depressive episode is therefore classified as bipolar II depression.

Symptom prevalence	General population (PSE)	Depressed patients (HAM-D6)
Most common	Depressed mood	Depressed mood/Work and interests
	Lack of energy	Tiredness and pains
	Worrying/Tension	Psychic anxiety
Least common	Guilt feelings	Guilt feelings
	Depression worst in the morning	Psychomotor retardation
	Suicide	

Table III. Hierarchical patterns of depression-related symptoms in a population study after Present State Examination (PSE), and in patients with depressive illness after the 6-item Hamilton Depression Rating Scale (HAM-D6). See comments in text.[18,23]

From: Sturt E. Hierarchical patterns in the distribution of psychiatric symptoms. *Psychol Med.* 1981;11:783-794.[17]

Is sadness the cause or consequence of depressive neurovegetative symptoms?

The HAM-D "general somatic" symptom, which includes tiredness, muscular tension, and pains, shares its phenomenology with the core symptoms of depressive states *(Tables III and IV),* in contrast to the neurovegetative symptoms of sleep, appetite, and autonomic anxiety (eg, cardiovascular, respiratory, and genitourinary symptoms).[22] In the Hamilton Anxiety Rating Scale (HAM-A), the autonomic anxiety symptoms are not among the core items of the symptomatic *DSM-IV* criteria for generalized anxiety disorder (GAD). Dose-response studies with selective serotonin reuptake inhibitors in patients with major GAD[23] or depression[24] indicate that only

DSM-IV or *ICD-10* symptoms of depression	Lack of energy
Depressed mood	0.52
Lack of interests	0.60
Low self-confidence	0.51
Guilt feelings	0.46
Life not worth living	0.34
Lack of concentration	0.47
Restlessness	0.45
Retardation	0.48
Sleep problems	0.31
Appetite problems	0.39

Table IV. Prevalence (Spearman correlation coefficients) of depressive symptoms over 2 weeks measured by the Major Depression Inventory in a general population (*N*=1121).

From: Olsen LR, Jensen DV, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. *Psychol Med.* 2003;33:351-356.[20]

the neurovegetative symptoms of tiredness and muscular tension have a shared phenomenology. These symptoms should not therefore be considered a consequence of depressed mood, but rather as reflecting an interactive manifestation of the "psychic" and the "somatic" items in the Hamilton scales.

In the HAM-D, the neurovegetative symptoms of affective disorder covering autonomic symptoms are combined into a single somatic anxiety item, whereas in the HAM-A they are listed individually and include cardiovascular, gastrointestinal, and genitourinary symptoms. Benzodiazepines and β-blockers have a specific effect on autonomic symptoms.[25] However, in patients with affective disorders, these classes of drugs often induce the core symptoms of depression once the autonomic symptoms have been reduced. In other words, autonomic symptoms were masking the depressive illness.

Depressed mood	HAM-D17 Conventionally	Empirically, mean (sd) HAM-D17	HAM-D6	MES
(*N*=689) 0 No	≤7	3.4 (3.1)	2.0 (1.9)	3.4 (3.1)
(*N*=748) 1 Doubtful	13	9.4 (3.7)	5.9 (1.8)	9.6 (3.3)
(*N*=1226) 2 Mild	18	16.2 (4.5)	9.6 (2.0)	16.3 (3.8)
(*N*=859) 3 Moderate	25	23.0 (4.7)	12.7 (1.9)	22.3 (3.7)
(*N*=190) 4 Severe	30	28.7 (5.0)	15.4 (2.1)	27.5 (4.8)

Table V. Standardization of the Hamilton Depression Scales HAM-D17 and HAM-D6, and Melancholia Scale (MES), using depressed mood as a global index (patients seen weekly: *N*=534; total data items: 3712).

Data sources: Lauritzen L, Odgaard K, Clemmesen L, et al. Relapse prevention by means of paroxetine in ECT-treated patients with major depression: A comparison with imipramine and placebo in medium-term continuation therapy. *Acta Psychiatr Scand.* 1996;94:241-251;[29] Bech P. Quality of life in psychosomatic research. A psychometric model. *Psychopathology.* 1987;20:169-179;[30] Martiny K, Lunde M, Undén M, Dam H, Bech P. Adjunctive bright light in non-seasonal major depression: results from clinician-rated depression scales. *Acta Psychiatr Scand.* 2005;112:117-125.[31]

Is mood modification the appropriate treatment for depression?

Using the PSE to screen patients with Parkinson's disease, Brown and MacCarthy[26] found that 25% had depressed mood, but very few had the other symptoms of the depression syndrome. They concluded that depressed mood lowered quality of life in Parkinson's disease, but did not require antidepressant medication, apart from a few exceptions. Many quality of life questionnaires include depressed mood. The *DSM-IV* criteria for depressed mood can be found in the Medical Outcome Study 36-item Short-Form Health Survey: "Have you felt so down in the dumps that nothing could cheer you up?"[27]

Sturt's general population study in the UK[17] found "depressed mood" to be one of the commonest symptoms measured by the PSE; "depression worst in the morning" was one of the least common *(Table III)*. However, in the PSE, "depressed mood" is in principle a score on a categorical scale (present versus not present), in contrast to the HAM-D, which it is measured on the 5-point scale from 0 to 4 *(Table IA)*. "Depressed mood worst in the morning" is, strictly speaking, not a symptom, but the course of a symptom. Diurnal variation in mood symptoms is an indicator for depressive illness and not for stress-related sadness. The Newcastle Diagnostic Depression Scale[28] includes diurnal symptom variation as an indicator of endogenous depression, alongside the important "quality of depression" item for which patients are asked to what extent their sadness is qualitatively distinct from normal despondency when under adversity or stress. In other words, they are invited to distinguish between "ordinary" sadness, as experienced in adverse situations (grief, ill-health etc), and the qualitatively different experience of being "depressed for no reason at all." Both "depressed mood regularly worse in the morning" and a distinct "quality of depression" are among the criteria for endogenous depression or "melancholic" features in *DSM-IV*.

In patients diagnosed with major depression and requiring antidepressant medication, mood modification is an important indicator of early treatment effect. Use of the dynamic item response theory model in antidepressant trials to identify specific improvement curves has shown that the total score of the six HAM-D6 items is a sensitive indicator of response. However, because the "depressed mood" item has the highest prevalence in the HAM-D6, it has most room for improvement and the greatest variance in response, often referred to as high responsiveness or sensitivity. Most antidepressant trials consider the "depressed mood" item *(Table IA)* a "global" indicator of response and therefore show it separately.

To illustrate "depressed mood" as a "global" indicator within the HAM-D, we standardized total scores on the HAM-D17, HAM-D6, and Melancholia Scale (MES) using data from baseline ratings as well as weekly ratings from different studies to cover the whole range of the 5-point "depressed mood" scale (not depressed; doubtfully depressed; mildly depressed; moderately depressed; severely depressed) *(Table V)*. These studies were based on 87 patients receiving electroconvulsive therapy,[29] 345 inpatients,[30] and 102 ambulatory patients.[31] Mean HAM-D6 and MES scores fully corresponded to the conventional standardization of these scales,[23] whereas agreement between HAM-D17 and the conventional cutoff scores was only approximate *(Table V)*.

"Depressed mood" on the HAM-D17 has proved quite sensitive as an outcome measure of response in antidepressant trials. Thus a placebo-controlled trial of paroxetine covering a fixed dose range of 10, 20, 30, and 40 mg daily found that not only was 20 mg the minimal effective dose, but that it was also superior to 30 mg and 40 mg on the HAM-D17.[32] On the HAM-D "depressed mood" item, 20 mg was also the minimal effective dose but the dose-response curve for 30 mg and 40 mg was flat. Paroxetine showed a clear linear dose-response relationship for adverse effects, which seemed to be reflected in the nonspecific HAM-D items.[32]

A dose-response study with fixed doses of venlafaxine (from 25 mg to 200 mg daily) versus placebo showed "depressed mood" on the HAM-D to be more sensitive than the HAM-D17 or the 10-item Montgomery-Åsberg Depression Rating Scale

(MADRS10),[33] demonstrating a dose-response relationship after only 1 week of therapy versus 3 to 4 weeks with the HAM-D17 and MADRS10. In patients with bipolar depression, lamotrigine 200 mg daily was superior to placebo on both HAM-D "depressed mood" and the global clinical improvement scale, but not on the HAM-D17.[34] Modification of depressed mood thus appears to be an appropriate treatment of depressive episodes in both unipolar and bipolar disorders. If reduction of the HAM-D17 items to half-a-dozen core items (HAM-D6) no longer appears so radical, what about a HAM-D2 version reduced simply to "depressed mood" and "work and interests"? We might eventually arrive at a HAM-D1 version reduced solely to "depressed mood" as a global impression score of depressive states. ❐

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. *(DSM-IV).* Washington, DC: American Psychiatric Association; 1994.
2. Vijayaraghavan L, Krishnamoorthy ES, Brown RG, Trimble MR. Abulia: a Delphi survey of British neurologists and psychiatrists. *Mov Disord.* 2002;17:1052-1057.
3. Berrios GE, Gill M. Abulia and impulsiveness revisited: a conceptual history. *Acta Psychiatr Scand.* 1995;92:161-167.
4. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol.* 1967;6:278-296.
5. Bech P, Kastrup M, Rafaelsen OJ. Mini-compendium of rating scales for states of anxiety, depression, mania, schizophrenia with corresponding DSM-III syndromes. *Acta Psychiatr Scand.* 1986; 73(suppl):7-37.
6. Guy W. *Early Clinical Drug Evaluation (ECDEU) Assessment Manual for Psychopharmacology.* Publication No. 76-338. Rockville, MD: National Institute of Mental Health; 1976.
7. Hamilton M, Shapiro CM. Depression. In: Peck DF, Shapiro CM, eds. *Measuring human problems.* Chichester, UK: John Wiley; 1990:25-65.
8. Beck AT, Ward CH, Mendelson M. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561-571.
9. Fava M, McCall WV, Krystal A, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry.* 2006;59:1052-1060.
10. Bech P. Rating scales in depression: limitations and pitfalls. *Dialogues Clin Neurosci.* 2006;8:207-215.
11. Bech P. *Rating scales for psychotherapy, health states and quality of life.* Berlin, Germany: Springer; 1993:164-165.
12. Clebsch WA. *American Religious Thought: A History.* Chicago, Ill: University of Chicago Press; 1973.
13. Ackroyd P. *T. S. Eliot.* London, UK: Hamish Hamilton; 1984.
14. Storr A. *Churchill's Black Dog and Other Phenomena of Human Mind.* Glasgow, UK: HarperCollins; 1997.
15. World Health Organization. *International Classification of Diseases, Tenth Revision (ICD-10). Diagnostic Criteria for Research.* Geneva, Switzerland: World Health Organization; 1993.
16. Wing JK, Babor T, Brugha T, et al. SCAN: Schedules for clinical assessment in neuropsychiatry. *Arch Gen Psychiatry.* 1990; 47:589-593.
17. Sturt E. Hierarchical patterns in the distribution of psychiatric symptoms. *Psychol Med.* 1981;11:783-794.
18. Bech P. Rating scales for affective disorders: their validity and consistency. *Acta Psychiatr Scand.* 1981:64(suppl):1-101.
19. Bech P, Allerup P, Gram LF, et al. The Hamilton Depression Scale. Evaluation of objectivity using logistic models. *Acta Psychiatr Scand.* 1981;63:290-299.
20. Olsen LR, Jensen DV, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. *Psychol Med.* 2003;33: 351-356.
21. Hjollund NH, Andersen JH, Bech P. Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. *Health Qual Life Outcomes.* 2007;5:12-16.
22. Benazzi F. Bipolar disorder—focus on bipolar II disorder and mixed depression. *Lancet.* 2007;369:935-945.
23. Bech P, Lunde M, Bech-Andersen G, Martiny K, Lindberg L. Psychiatric outcome studies (POS): does treatment help the patients? A Popperian approach to research in clinical psychiatry. *Nord J Psychiatry.* 2007;61(suppl 46):1-80.
24. Bech P, Andersen HF, Wade A. Effective dose of escitalopram in moderate versus severe *DSM-IV* major depression. *Pharmacopsychiatry.* 2006;39:128-134.
25. Rickels K, Downing R, Schweizer E, Hassman H. Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry.* 1993;50:884-895.
26. Brown RG, MacCarthy B. Psychiatric morbidity in patients with Parkinson's disease. *Psychol Med.* 1990;20:77-87.
27. Tarlov AR, Ware JE Jr, Greenfield S, et al. The Medical Outcomes Study. An application of methods for monitoring the results of medical care. *JAMA.* 1989;262:925-930.
28. Carney MWP, Roth M, Garside RF. The diagnosis of depressive syndromes and the prediction of ECT response. *Br J Psychiatry.* 1965:111:659-674.
29. Lauritzen L, Odgaard K, Clemmesen L, et al. Relapse prevention by means of paroxetine in ECT-treated patients with major depression: A comparison with imipramine and placebo in medium-term continuation therapy. *Acta Psychiatr Scand.* 1996;94: 241-251.
30. Bech P. Quality of life in psychosomatic research. A psychometric model. *Psychopathology.* 1987;20:169-179.
31. Martiny K, Lunde M, Undén M, Dam H, Bech P. Adjunctive bright light in non-seasonal major depression: results from clinician-rated depression scales. *Acta Psychiatr Scand.* 2005;112: 117-125.
32. Dunner DL, Dunbar GC. Optimal dose regimen for paroxetine. *J Clin Psychiatry.* 1992;53(suppl):21-26.
33. Mendels J, Johnston R, Mattes J, Riesenberg R. Efficacy and safety of b.i.d. doses of venlafaxine in a dose-response study. *Psychopharmacol Bull.* 1993;29:169-174.
34. Calabrese JR, Bowdan CL, Sachs GS, Ascher JA, Monagahn E, Rude GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. *J Clin Psychiatr.* 1999;60:79-88.

L'HUMEUR DÉPRESSIVE, SYMPTÔME MAJEUR DE LA DÉPRESSION

La tristesse ou l'humeur dépressive représente le principal symptôme spécifique de l'état dépressif, comme le montrent la plupart des études utilisant l'échelle HAM-D (Hamilton Depression Rating Scale). *Que ce soit dans le* DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) *ou l'*ICD-10 (International Statistical Classification of Diseases and Health-Related Problems, 10th Revision), *« humeur dépressive » et « perte d'intérêt ou de plaisir dans presque toutes les activités » sont les deux « grands » symptômes de la dépression majeure. Ces deux items se superposent dans le concept d'aboulie qui recouvre l'anhédonie et l'humeur dépressive. Les symptômes neurovégétatifs associés aux états dépressifs doivent être considérés comme une manifestation interactive de l'évolution de la maladie mais dont le score est moins spécifique que l'humeur dépressive ou l'anhédonie. L'humeur dépressive ne doit donc pas être considérée comme une conséquence des symptômes neurovégétatifs. Les modifications de l'humeur dépressive sont le meilleur indicateur de l'effet antidépresseur. Beaucoup des symptômes neurovégétatifs présents dans l'HAM-D pourraient n'être que le reflet des effets indésirables du traitement antidépresseur, alors que le symptôme « humeur dépressive », évalué séparément, est l'indicateur le plus sensible de l'effet antidépresseur. Ceci a été confirmé dans de nombreuses études contrôlées contre placebo. L'humeur dépressive, lorsqu'elle est utilisée comme indicateur de sévérité globale, montre une standardisation satisfaisante entre les différentes échelles d'évaluation des symptômes. Ainsi, si nous devions opter pour une échelle HAM-D1 (c'est-à-dire avec seulement un item et non une demi douzaine comme dans l'HAM-D6, sous-échelle de l'HAM-D17), cet item unique serait indubitablement « l'humeur dépressive ».*

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Negative symptoms in depression: from anhedonia to retardation

by R. Jouvent, France

The core features of depression can be observed across several domains, including those related to affective, cognitive, motor, and circadiansomatic function. Typical affective symptoms are anhedonia (loss of pleasure) and emotional blunting. These negative symptoms, in addition to the cognitive symptoms of depression, may be viewed as resulting from the impairment of a system underlying volition. This impairment may reflect both a primary disorder of volitional operation and deficits in processes associated with the initiation of action and allocation of attentional resources during cognitive effort. This paper emphasizes the role of cognitive flexibility and the capacity to mobilize cognitive resources to explain the cognitive control deficits and emotional dysregulation observed in depression with anhedonia and psychomotor retardation.

Anhedonia, a personality trait defined as a decreased capacity to experience pleasure, can be viewed, together with depression, as resulting from specific deficits in a system underlying volition located in several regions of the prefrontal cortex. We discuss the hypothesis that volitional and cognitive deficits in anhedonia and depression are two facets of a same process that consists in the failure to maintain emotional and cognitive control in times of increased and sustained cognitive demands. According to this view, the deficits observed in depressed patients with anhedonia and psychomotor retardation when faced with an effortful task are preceded by an increase in the effort required to maintain a high level of performance. Such patients recruit more cognitive resources than controls during cognitive effort, to an extent that may deplete their cognitive and brain resources. Cognitive resource exhaustion may thus account, at least in part, for the impaired volition seen in this depressive subgroup.

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Keywords: *anhedonia; depression; retardation; cognitive dysfunction; negative symptom; dopamine; cognitive effort; emotion*

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Emotional deficit: anhedonia

Depression is associated with a variety of emotional disturbances, and has been subgrouped on this basis. In particular, we have defined two contrasting emotional subgroups: depressed patients with anhedonia and psychomotor retardation, versus those with anxiety, agitation, and hyperemotivity.[1] This distinction may have a pathophysiological basis: using functional imaging, we have shown that a decrease in presynaptic dopamine function in the left caudate nucleus is found only in anhedonic depressives with retardation.[2] During treatment of a depressive episode, these clinical dimensions can progress independently of other symptoms.[3]

Cognitive deficit: psychomotor retardation

More recently, several studies have revealed the cerebral cost of depression on the functional, anatomic, and cognitive-emotional levels. Depression leaves neuronal and functional scars. On the functional level, it is associated with impaired cerebral dynamics, measured by indices extracted from electroencephalography (EEG) signals. During the depressive episode, cerebral dynamics are more predictable and rigid; they are less inclined to adapt and adjust by incorporating new elements. Depression is characterized by a reduction in the variety, complexity, and instability, hence richness, of neuronal dynamics.[4]

Many cerebral imaging studies have shown dysfunction, in particular in the dorsolateral prefrontal cortex, but also in the amygdala and hippocampus. Thus, depressed patients show hypoactivation while performing a verbal fluency task consisting of uttering as many words beginning with "P" as possible within a set time.[5] Morphological data confirm the cumulative effect of depressive episodes. Studies using neuroimaging, experimental pharmacol-

ogy, and postmortem observation have shown volume reductions or structural abnormalities in many brain regions known to be involved in depression, primarily in cortical and striatal gray matter and hippocampus.[6]

These results are explained by changes in neuroplasticity, neurogenesis, and cell resilience in depression. The effects of antidepressants on synaptic plasticity support this hypothesis: antidepressants increase neurotrophic factors and neurogenesis.[7] For example, in the hippocampus, antidepressants increase both the proliferation and survival of young hippocampal cells.[8,9]

Recent review has suggested that these morphological and structural changes in depression are largely responsible for the deterioration in cognitive function.[10] The damage is cumulative and leaves scars between episodes. The more frequent the dysthymic episodes, the more the cognitive disorders persist and intensify.[11]

Memory is the most frequently impaired function, usually in correlation with episode severity or frequency.[12] Memory impairment suggests a strategy disorder, with difficulties in generating cognitive and behavioral diversity.[13]

Signs and symptoms may serve as a guide, but are inadequate for describing the cognitive deficit. Loss of memory and impaired concentration are familiar depressive symptoms for psychiatrists. An array of experimental data suggests that negative symptoms (anhedonia, blunted affect, retardation) in depression are associated with more profound cognitive deficits. The manifestations of depression are extremely heterogeneous. Decreased activation in the dorsolateral region of the prefrontal cortex is associated more with the presence of psychomotor retardation than with depression severity.[14] Further evidence is that the most retarded depressives are those with the severest attention deficit, whereas moderately retarded depressives have less severe attention deficits.[15]

The most consistently observed feature of depression-related cognitive deficit is the preservation of performance in relatively simple tests, in contrast to a deterioration in performance when tasks become more complex *(Figure 1).*[16,17] This is explained by the coexistence of three types of executive dysfunction:

◆ *Sustained attention deficit.* Attention is a fluctuating state, exercised in space and time. Its temporal aspect involves the processes of orientation reaction, reflex capture, and maintenance of attention over time. Decrease in attention represents the degree of decline in performance over time.[18] A feature specific to depressives is that they can begin a task normally, but very soon become exhausted: they can play table tennis or chess for only 20 or 30 seconds at their normal level before their performance declines.

◆ *Impaired memory.* Deficits are observed in verbal, working, visuospatial, and autobiographic memory, with a consistency that varies between tests and the patient populations used.[19,20] The feature common to each memory deficit appears to be the effortful character of the tasks involved.

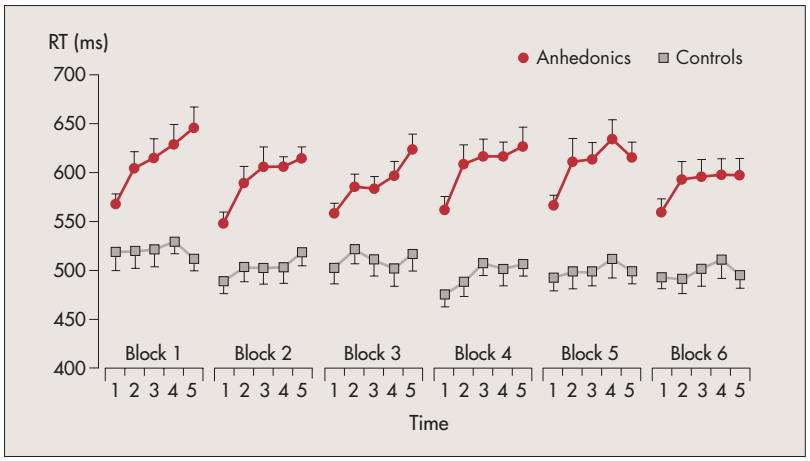

Figure 1. Mean reaction times (RTs) according to time-on-task. Subjects completed six blocks of 100 trials each. Each block lasted about 5 minutes. Blocks were separated by a 2-minute pause. The whole task lasted about 40 minutes.

Reproduced from reference 16: Dubal S, Jouvent R. Time-on-task effect in trait anhedonia. *Eur Psychiatry.* 2004;19:285-291. Copyright © 2004, Elsevier Masson SAS.

◆ *Cognitive inhibition.* Executive functions identify the best strategies within the behavioral spectrum for responding to environmental stimuli. Above all they allow rapid interplay between controlled and automatic processes. Planning, cognitive flexibility, and the ability to change or alternate motor and conversational strategies all play a very important role in this regard.[21]

Two facets of the same process?

There is every indication that cognitive deficits and emotional impairment in depressives are simply two facets of one and the same process. We can safely hypothesize that depression is a long process comprising a constellation of emotional and cognitive adjustments and maladjustments, all of which may account for the progressive anhedonia. The thought machine appears rusty and less fluid, with the result that psychic pleasure and reinforcement are decreased. The same applies to social pleasure. Defective interpersonal relations have long been documented in depressives. These subclinical symptoms have themselves a negative impact on social functioning, hedonism, and quality of life. Anhedonia and retardation thus appear to act on each other in a vicious circle.

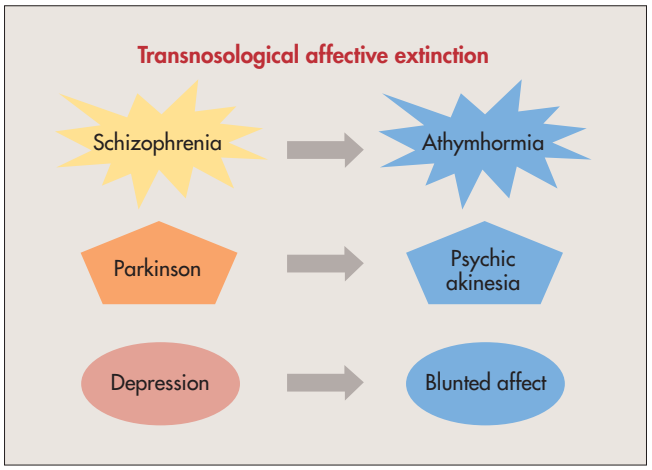

Figure 2. Transnosological affective extinction.

◆ *Extending to transnological approach*

This combination of emotional and cognitive approaches may lead to a dimensional, transnosographic view of negative symptoms. Indeed, negative symptoms can be found across various nosographic categories. However, in each pathological setting, negative symptoms are "indexed," or "colored," by nosological specificities *(Figure 2, page 15)*.[22]

Conclusion

Cognitive impairment is characteristic of both depressives and anhedonic healthy subjects. Depressives and anhedonic patients recruit more cognitive resources than controls during cognitive effort. Repeating such cognitive effort may consume the requisite brain resources. Volitional deficit in depression and loss of pleasure in anhedonia may partially reflect this exhaustion of cognitive resources. Going a step further, we can hypothesize that both retarded anhedonic depressives have two important reasons for developing a specific negative pattern. In the brain, foci of network dysfunction identified in the baseline depressed state should be considered as etiological abnormalities as well as sites of adaptive intrinsic compensatory processes. A given metabolic or brain activation pattern (assessed by positron emission tomography or functional magnetic resonance imaging) is a combination of a functional lesion and an ongoing process of attempted self-correction or adaptation.

From this perspective, net regional activity is what accounts for the observed clinical symptoms. For instance, frontal hyperactivity could be seen as an exaggerated and maladaptive compensatory process, manifesting clinically as psychomotor agitation and rumination, the purpose of which is to override, at cortical level, a persistent negative mood generated by abnormal chronic activity of limbic subcortical structures. In turn, frontal hypometabolism might reflect the failure to initiate or to maintain such a compensatory state with resulting apathy, anhedonia, and impaired executive functioning. ❒

REFERENCES

1. Jouvent R. Physiopathologic hypotheses of depression. *Encephale*. 2000;26(special issue):57-59.
2. Paillère-Martinot ML, Bragulat V, Artiges E, Dollé F, Hinnen F, Jouvent R, Martinot JL. Decreased presynaptic dopamine function in the left caudate of depressed patients with affective flattening and psychomotor retardation. *Am J Psychiatry*. 2001;158: 314-316.
3. Jouvent, R, Le Houezec, J, Payan, et al. Dimensional assessment of onset of action of antidepressants : a comparative study of moclobemide vs clomipramine in depressed patients with blunted affect and psychomotor retardation. *Psychiatry Res*. 1998;79: 267-275.
4. Pezard L, Martinerie J, Muller-Gerking J, Varela FJ, Renault B. Entropy quantification of human brain spatio-temporal dynamics. *Physica D*. 1996;96:344-354.
5. Okada G, Okamoto Y, Morinobu S, Yamawaki S, Yokota N. Attenuated left prefrontal activation during a verbal fluency task in patients with depression. *Neuropsychobiology*. 2003;47:21-26.
6. Fossati P. A functional brain imaging perspective in depression. *Medicographia*. 2008;30:00-00.
7. Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff K, Gray NA, Zarate CA, Charney DS. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol Psychiatry*. 2003;53:707-742.
8. Manev H, Uz T, Smalheiser NR, Manev R. *Eur J Pharmacol*. 2001;411:67-70.
9. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*. 2003;301:805-809.
10. Rogers MA, Kasai K, Koji M, Fukuda R, Iwanami A, Nakagome K, Fukuda M, Kato N. Executive and prefrontal dysfunction in unipolar depression: a review of neuropsychological and imaging evidence. *Neurosci Res*. 2004;50;1-11.
11. Kessing LV, Andersen PK, Mortensen PB, Bolwig TG. Recurrence in affective disorder. I. Case register study. *Br J Psychiatry*. 1998;172:23-28 */— and/or —/* Kessing LV. Recurrence in affective disorder. II. Effect of age and gender. *Br J Psychiatry*. 1998; 172:29-34.
12. Basso MR, Bornstein RA. Relative memory deficits in recurrent versus first-episode major depression on a word-list learning task. *Neuropsychology*. 1999;13:557-563.
13. Fossati P, Hevenor SJ, Lepage M, Graham SJ, Grady C, Keightley ML, Craik F, Mayberg H. Distributed self in episodic memory: neural correlates of successful retrieval of self-encoded positive and negative personality traits. *Neuroimage*. 2004;22:1596-1604.
14. Dolan RJ, Bench CJ, Brown RG, Scott LC, Friston KJ, Frackowiak RS. Regional cerebral blood flow abnormalities in depressed patients with cognitive impairment. *J Neurol Neurosurg Psychiatry*. 1992;55:768-773.
15. Lemelin S, Baruch P. Clinical psychomotor retardation and attention in depression. *J Psychiatr Res*. 1998;32:81-88.
16. Dubal S, Jouvent R. Time-on-task effect in trait anhedonia. *Eur Psychiatry*. 2004;19:285-291.
17. Hartlage S, Alloy LB, Vazquez C, Dykman B. Automatic and effortful processing in depression. *Psychol Bull*. 1993;113:247-278.
18. Parasuraman R. Sustained attention in detection and discrimination. In: Parasuraman R, Davis DR, eds. *Varieties of Attention*. New York, NY: Academic Press; 1984:243-271.
19. Elliott R, Sahakian BJ, McKay AP, Herrod JJ, Robbins TW, Paykel ES. Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. *Psychol Med*. 1996;26:975-989.
20. Ellwart T, Rinck M, Becker ES. Selective memory and memory deficits in depressed inpatients. *Depression Anxiety*. 2003;17: 197-206.
21. Petty SC, Sachs-Ericsson N, Joiner TE. Interpersonal functioning deficits: temporary or stable characteristics of depressed individuals? *J Affect Disord*. 2004;81:115-122.
22. Derouesné C, Jouvent R. Dimensional versus nosographic approach to Alzheimer's disease: therapeutic implications. *Neuroepidemiology*. 1990:9:177-182.

SYMPTÔMES NÉGATIFS DANS LA DÉPRESSION : DE L'ANHÉDONIE AU RALENTISSEMENT PSYCHOMOTEUR

L'anhédonie est un trait de personnalité qui se définit par la diminution de la capacité à éprouver du plaisir. Elle peut être considérée, avec la dépression, comme résultant de déficits spécifiques du système sous-tendant la volition, dont la localisation est répartie dans plusieurs régions du cortex préfrontal. Nous proposons l'hypothèse selon laquelle les déficits volitifs et cognitifs à l'origine de l'anhédonie représentent deux facettes d'un unique processus qui se traduit par l'incapacité à assurer le contrôle émotionnel et cognitif lorsque surviennent des stimuli cognitifs augmentés et prolongés. Selon cette hypothèse, une augmentation de l'effort nécessaire pour maintenir un niveau élevé de performance précéderait la survenue des déficits observés chez les patients déprimés présentant une anhédonie et un ralentissement psychomoteur qui sont confrontés à des tâches requérant un effort. Ces patients doivent mobiliser plus de ressources cognitives que les sujets contrôles au court de l'effort cognitif, au risque d'épuiser leurs ressources cognitives et cérébrales. L'épuisement des ressources cognitives rendrait ainsi compte, en partie du moins, de l'altération de la volonté observée dans ce sous-groupe de patients dépressifs.

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Disturbed sleep as a core symptom of depression

by P. Monteleone and M. Maj, Italy

Subjective sleep disturbance, typically sleep-onset insomnia, frequent nocturnal awakening, early morning awakening and, less typically, hypersomnia, is common in major depression. It also includes structural polysomnographic changes, mainly increased "pressure" of rapid eye movement sleep and decreased slow-wave sleep. Although none of these changes appear specific to depression, some persist after remission, representing a putative marker of vulnerability. Epidemiological data suggest that sleep disturbance is not only a core symptom of depression, but also represents a risk factor or prodromal symptom of a new depressive episode, or a residual symptom after successful treatment. Management of insomnia is thus an important component in the prevention and treatment of depression. Antidepressants differ both between and within drug classes in their effects on subjective sleep and sleep architecture. Clinicians need to take these effects into account when choosing the most appropriate antidepressant for a given patient.

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Keywords: *antidepressants; depression; risk factor; sleep architecture; sleep disturbance*

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Sleep pattern changes were first associated with depression over 30 years ago.[1] Between 50% and 90% of diagnosed depressives complain of sleep disturbance,[2-4] typically sleep-onset insomnia, frequent nocturnal awakening, and early morning awakening. Although none of these complaints are pathognomonic of depression, sleep onset insomnia is usually viewed as the least specific, and early morning awakening as the most specific. Hypersomnia is less typical, although it may occur in certain subtypes, such as bipolar depression, seasonal affective disorder, and atypical depression;[5-7] it is more common in younger depressives, especially women.[8] Sleep disturbance is such a fundamental aspect of depression that the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV)* criteria for major depressive episode include "insomnia or hypersomnia nearly every day." Insomnia, in particular, is one of the most frequent and prominent symptoms, and often the presenting complaint in depression. Not only is it typical, but it may also represent a risk factor or prodromal symptom of a new depressive episode or a residual symptom after successful treatment. This article reviews current knowledge of sleep disturbance in depression, discusses its biological background, and examines its response to antidepressant drugs.

Sleep disturbance in depression

Depression-related insomnia comprises subjective sleep disturbance but also abnormal sleep architecture, as first shown by Kupfer and colleagues[1,9] in the early 1970s. Polysomnography reveals impaired sleep continuity and duration, reduced slow-wave sleep (SWS), shortened rapid eye movement (REM) sleep latency, an increased proportion of REM sleep in the early part of the night, a prolonged first REM period, increased total REM sleep, and increased eye movement counts during REM periods (REM density). Shortening of the interval between sleep onset and first REM period from 90 min in normal subjects to between 20 min and 30 min (decreased REM sleep latency) was initially proposed as a biological marker of primary depression, unrelated to any other mental or organic disorder.[10] Reanalysis

SELECTED ABBREVIATIONS AND ACRONYMS

Ach	acetylcholine
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*
5-HT	serotonin
NE	norepinephrine
NREM	nonrapid eye movement
REM	rapid eye movement
SAD	seasonal affective disorder
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective norepinephrine reuptake inhibitor
SWS	slow-wave sleep
TCA	tricyclic antidepressant

of the original data by the same group,[11] however, showed that patients with secondary depression, due to other disease, also had REM latencies within the range seen in primary depression. They concluded that the initial differences had been an artifact of the differing age distribution between the two patient groups.

Subsequent studies addressed the differential diagnostic value of short REM latency and/or other REM sleep abnormalities for a specific subtype of depression. Some found no significant differences in REM sleep changes between endogenous/melancholic depression (a subtype with more somatic features and a biological substrate) and nonendogenous depression.[12-14] Others found reduced REM sleep latency specific for endogenous depression.[15-17] However, since the latter compared less severely nonendogenously depressed patients with more severely depressed endogenous patients, the discrepancy could be explained by the impact of depression severity on sleep. Similarly, the greater severity of depression with psychotic features could account for the reportedly greater REM sleep abnormalities in psychotic versus nonpsychotic depression.[1,18,19] Studies of unipolar versus bipolar depression have found no significant polysomnographic differences.[17,20] Thus the burden of present evidence is that REM sleep changes are not specific to depression subtypes. Decreases in REM sleep latency and SWS also occur in other psychiatric disorders. Meta-analysis of 177 sleep laboratory studies in various psychiatric syndromes found that the reduced sleep efficiency and total sleep time accounted for by the decreases in REM sleep disinhibition and SWS were not highly specific to affective disorders. They also occurred in other psychiatric conditions, such as schizophrenia, alcoholism, obsessive-compulsive disorder, and dementia.[21]

A key point is whether sleep abnormalities in depression are "state-" or "trait-dependent." Longitudinal studies of EEG sleep profiles in depression described a tendency for REM sleep abnormalities to resolve with remission,[22,23] and total normalization was even reported after successful treatment.[24] This was consistent with the assumption that polysomnographic abnormalities were a state-dependent phenomenon. However, other studies reported persistence of REM sleep abnormalities during remission,[25,26] and found an association between short REM latency during remission and an increased risk of relapse.[27] Persistence of reduced SWS was similarly associated with more rapid and frequent recurrence.[28]

Since antidepressants modify sleep architecture, these results could be biased by the inclusion of drug-treated patients. To control for such an effect, sleep profiles were longitudinally assessed in depressed patients undergoing cognitive-behavioral therapy. Decreased REM sleep latency, decreased delta sleep ratio (the ratio of delta wave counts in the first and second non-REM [NREM] sleep periods), and decreased SWS were found to be stable over time, whereas REM density and sleep efficiency improved significantly with remission.[29] These findings suggest that at least some polysomnographic changes represent a marker of "vulnerability" to depression. In support of this view, healthy subjects with no personal history, but a heavy family history of depression, were found to exhibit increased REM density and decreased SWS,[30] while relatives of depressed probands with short REM latency were found to have a lifetime risk of depression almost double that of relatives of depressed probands with normal REM latency.[31] Increased REM density in healthy relatives of depressed patients was recently reported to be predictive of a psychiatric disorder,[32] suggesting that this polysomnographic alteration may constitute a vulnerability marker.

Although *DSM-IV* includes hypersomnia in the criteria for major depressive episode, it is a less common feature. It is mostly related to subtypes such as bipolar depression, atypical depression, and seasonal affective disorder (SAD).[6,33,34] Polysomnographic studies in depressives with hypersomnia are relatively scanty. Patients with atypical depression exhibit completely normal polysomnograms if wakened relatively early in the morning. But if allowed to sleep to satiety, they show long total sleep time, with a normal amount of SWS and more REM sleep than normal, probably because their longer sleep time results in one or two more REM sleep episodes.[35] Length of sleep in SAD does not differ greatly from that in the general population, but sleep patterns differ from those of other patients with major depression since they exhibit significantly longer NREM episodes and greater slow-wave activity during NREM sleep.[36,37] Hypersomnia in depression remains difficult to quantify, and complaints of hypersomnolence often involve excessive daytime sleepiness as a consequence of depression- or treatment-related nocturnal insomnia. Drug strategy should be careful to take its presence into account.

The incidence and severity of sleep disturbance in depression appear strongly influenced by age, gender, and depression severity. In healthy subjects, age is itself a well-recognized cause of sleep changes, in particular increased nocturnal awakening, decreased SWS, early morning awakening, and shorter REM latency.[38,39] Most studies in depression have shown negative correlations between REM latency and age, whereas REM density appears unrelated to age.[14,40,41] Differences between patients and controls may be more prevalent among younger adults and diminish with increasing age.[42,43] As for gender, depressed men appear to have less SWS than their female counterparts[44]; the regulation of slow-wave activity was impaired in depressive men, but not women.[42,43] Some studies have claimed correlations between sleep abnormalities and depression severity, measured by psychometric scales,[17,22,45] but these remain unconfirmed.[16,46]

Sleep disturbance and the risk of depression

Individuals with sleep disturbance may be at high risk for depression over the subsequent 1-3 years. Of 7900 participants in the Epidemiologic Catchment Area study, 40% of those with insomnia and 46%

of those with hypersomnia in the previous 6 months met criteria for a psychiatric disorder, with major depression showing the strongest association with sleep disturbance.[47] At reinterview a year later, 14% of those with persistent insomnia had a new episode of major depression, representing a near 40-fold greater risk than in those without sleep complaints. Conversely, individuals whose insomnia had resolved before the 1 year follow-up had much less chance of developing depression. In a subsequent analysis of the same data set, insomnia at a given time point identified 47% of new cases of major depression in the following year, thus having the strongest predictive value of all the symptoms considered.[48]

Epidemiological data from primary care show a quadruple increase in the likelihood of depression in patients with severe insomnia.[49,50] A similar analysis of 1000 adults followed for 3 years in a managed care organization confirmed that a history of insomnia at baseline conferred a relative risk of 4.0 for new onset major depression.[51] Of eight epidemiological studies of baseline primary insomnia as a predictor of depression, all but one suggested that isolated insomnia predicted an increased risk of depression in the following 1-3 years.[52] Similarly, meta-analysis of 20 prospective studies of risk factors for depression among community elderly showed that sleep disturbance was one of the strongest predictors of depression over a mean 2-year follow-up.[53]

Studies confined to 1-3–year follow-up cannot exclude baseline insomnia as just an early prodrome of ensuing depression. However, preliminary epidemiological data suggest that the elevated risk for mood disorders associated with disturbed sleep is not limited to 1 to 3 years, but may persist for a lifetime. In a prospective 40-year study of the relationship between self-reported sleep disturbance and subsequent depression in 1053 medical students, 12% reported clinical depression at some time in adulthood; those reporting insomnia in medical school had twice the risk of clinical depression.[54] Although these findings require replication, they suggest that insomnia in young adults remains a predictor of depression over at least 30 years. Indeed, chronic insomnia itself may trigger depression: inability to sleep as desired may cause helplessness-hopelessness feelings leading to depression. These data emphasize the need for appropriate early treatment of sleep disorders to prevent subsequent depression.

Even today, only one third of patients remit fully from drug therapy. Another third are partial responders, and the remaining third nonresponders.[55] Partial responders still have residual symptoms. These are associated with poor outcomes such as relapse, work impairment, and emotional distress.[56-59] Sleep disturbance persists in many partial responders: early insomnia in 48%, middle insomnia in 53%, and late insomnia in 16%.[58] However, because many drugs interfere with sleep,[35] assessment of residual sleep disturbance must control for treatment-emergent disturbance. In a study where 44% of patients meeting the criteria for remission continued to complain of sleep disturbances, almost all had had sleep disturbance on starting treatment, thus making it unlikely that the disturbance was treatment-emergent.[60] Residual sleep disturbance predicts relapse[61]: residual symptoms confer a 3- to 6-fold higher risk of relapse than full remission.[55] Clinicians thus need to be vigilant in identifying and treating residual sleep disturbance in the management of depression.

Persistent sleep disturbance appears associated with increased suicide risk, although few studies have addressed this issue. Reduced sleep for 4 weeks was highly predictive of further suicidal episodes in 58 high-risk patients with multiple acts of suicidal behavior.[62] In adolescents, suicidal ideation was linked to nonspecific somatic complaints, including sleep difficulties,[63] while depression and sleep difficulties in adolescent suicide attempters admitted to pediatric units were more frequent than in other inpatient settings.[64] The relationship between sleep disturbance and suicide risk in depression deserves further investigation.

Psychobiology of sleep disturbance in depression

The two most prominent explanations for the sleep abnormalities in depression are the reciprocal interaction model of NREM and REM sleep regulation[65] and the chronobiological paradigm based on the two-process Borbély model.[66]

The reciprocal interaction model assumes that sleep disturbance in depression is due to dysfunction of the central neurotransmitter systems—acetylcholine (Ach), norepinephrine (NE), and serotonin (5-HT)—that modulate mood and sleep/wakefulness. 5-HT neuron activity in the dorsal raphe nucleus and 5-HT release at serotonergic terminals are maximal during wakefulness, decreased during SWS, and minimal during REM sleep.[67,68] In animal studies, 5-HT neurons in the dorsal raphe (and noradrenergic neurons in the locus coeruleus) inhibit REM sleep (REM "off" neurons), whereas Ach neurons in the pontine tegmentum stimulate REM sleep (REM "on" neurons).[69] Thus, REM sleep regulation depends on a balance between the 5-HT/NE and Ach systems at the pontine level. Since depression has been strongly associated with increased central Ach tone and decreased 5-HT and NE transmission,[70] this imbalance has been held responsible for disinhibiting REM sleep in depressed individuals. The model was subsequently modified on the grounds that the neurotransmitter network involved in modulating REM sleep is not confined to the mesencephalon, but spread widely throughout the nervous system.[71]

There is evidence of cholinergic supersensitivity in depression, resulting in enhanced REM sleep pressure. Even in healthy humans, potentiation of brain Ach transmission shortens REM sleep latency and decreases SWS.[12] Compared with healthy controls, depressed patients exhibit shorter onset of REM sleep periods following cholinergic stimulation, although this effect does not appear depression-specific; great interindividual variability within both depressed and control groups is also

common.[72,73] Moreover, cholinergic stimulation with arecoline provoked faster REM sleep induction in remitted depressed patients than in healthy subjects,[74] while euthymic subjects with a family history of affective disorders showed an enhanced response of the REM sleep system to cholinergic stimulation.[75] These findings suggest that cholinergic supersensitivity leading to disinhibition of REM sleep may represent a trait or vulnerability marker of depression.

The chronobiological model focuses on NREM sleep rather than on REM-sleep disinhibition to explain sleep disturbance in depression. In the two-process model,[76] the amount of SWS at night is determined by the amount of prior wakefulness, the level of sleep propensity during the day, and the depth of sleep at night ("process S" ["sleep"]). Process S accumulates during waking hours as SWS propensity rises, and dissipates during the night, leading to an exponential decline in SWS. The second process ("process C" ["circadian"]) reflects the circadian control of sleep propensity, which is highest between 3 and 5 AM and lowest at 4 PM. The tendency to fall asleep depends on the difference between S and C; awakening occurs when S and C fall together. In healthy humans, the propensity for REM sleep is assumed to increase as SWS dissipates, thus explaining the short duration of the first REM period, when SWS is high (first part of the night), and the increase in REM sleep in the second part of the night, when SWS dissipates. In depression, the theory is that an impaired process S decreases SWS, with diminished accumulation of sleep pressure during the day and reduced dissipation of SWS at night.[66] The decrease in SWS in the initial NREM sleep period allows early onset of the first REM period.

The reciprocal interaction model of NREM and REM sleep regulation accounts for REM sleep timing abnormalities, but does not address NREM sleep disturbance per se, except as a consequence of REM disinhibition. The chronobiological impaired process S model, on the other hand, accounts for abnormal timing of sleep onset, intermittent nocturnal awakening, decreased SWS, and abnormal REM timing. It also accounts for the antidepressant effects of sleep deprivation by proposing that prolonging wakefulness increases process S and SWS, thereby ameliorating mood. Although each model has limitations, they remain possible explanations for abnormal sleep architecture in depression.

Effects of antidepressants on sleep in depression

Most antidepressants, whether tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), selective serotonin reuptake inhibitor (SSRI), or the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine, suppress REM sleep, prolong REM latency, and decrease total REM sleep time.[77] Due to the connection between increased REM sleep pressure and depression, antidepressant suppression of REM sleep was initially considered a precondition of efficacy.[77] This belief was backed by evidence of a correlation between the clinical response to amitriptyline and clomipramine and the degree of REM sleep suppression.[78,79] Furthermore, a study using selective REM sleep deprivation showed a significant correlation between improvement in depressive symptoms and REM sleep suppression.[80] However, not all antidepressants suppress REM sleep.[4,81] Atypical antidepressants, eg, the reversible MAOI moclobemide, nefazodone, and bupropion, may actually enhance REM sleep despite proven antidepressant efficacy.[82-84] This invalidates the hypothesis that antidepressants act by suppressing REM sleep. Antidepressants have less evident and consistent effects on NREM sleep parameters, with some drugs increasing SWS and others decreasing it.[77]

Antidepressant effects on sleep are clinically important. TCAs, for example, have very varied effects on subjective sleep. Amitriptyline, trimipramine, nortriptyline, and doxepin improve insomnia, whereas imipramine and desipramine are associated with insomnia; the evidence is less clear for clomipramine.[85] SSRIs have varied effects, with 10% to 15% of patients complaining initially of insomnia; as a result, a significant minority receive concomitant hypnotics. In a retrospective study of the Texas Medicaid database, 35% of 30 000 patients receiving SSRIs also received anxiolytic hypnotics.[86] Nevertheless, many patients report improved sleep during SSRI therapy.[87] The two SNRIs now available, venlafaxine and duloxetine, resemble SSRIs in their effects on sleep, with insomnia rates higher than placebo.[89,90]

Bupropion is generally considered an activating antidepressant, with 5% more patients reporting treatment-emergent insomnia than on placebo.[91] Mirtazapine significantly shortens time to sleep onset, improves sleep efficiency, and increases total sleep time by reducing nocturnal awakening, partly because of its prominent antihistaminic effects.[92]

Trazodone increased total sleep time and decreased nocturnal awakening.[93] It also improved insomnia when coprescribed with another antidepressant drug.[94,95] Nefazodone tends to improve sleep continuity and maintenance: in two double-blind studies it was more effective than fluoxetine in improving sleep quality and efficiency and in reducing nocturnal awakening.[96,97]

Agomelatine, an antidepressant with an innovative pharmacological profile combining melatonin receptor agonism and 5-HT_{2C} receptor antagonism, has peculiar effects on sleep architecture and subjective sleep in major depression. It increases SWS and normalizes the distribution of both SWS and REM sleep throughout the night, improving sleep continuity.[98] It was more effective than venlafaxine in terms of shorter sleep onset and greater sleep quality, without diurnal drowsiness.[99]

Antidepressants thus vary between and within classes in their effects on the sleep profile. Clinicians should allow for these effects when prescribing. Patients reporting sleep onset insomnia are more likely to benefit from a sedating antidepressant, whereas those complaining of hypersomnolence would benefit from a nonsedating compound.

Conclusion

Sleep disturbance is frequent in depression, but whether as cause or effect remains unknown. Nor is it yet clear whether sleep abnormalities are state or trait markers of major depression. At least some polysomnographic changes probably reflect "vulnerability," since not only do they fail to resolve on remission, but they are also present in never-depressed healthy subjects with a heavy family history of depression and in the healthy relatives of depressed probands. Genetic studies should aid understanding of the biological background to those abnormalities. Despite the absence of hard evidence for a causal relationship with depression, sleep disturbance deserve clinical attention. Nondepressed individuals with persistent insomnia appear at high risk for depression in the subsequent 1 to 3 years and for up to 30 years. Moreover, the persistence of sleep abnormalities in responders and remitters appears associated with increased risk of relapse, recurrence, and suicide. Optimized management of insomnia may thus play an important part in the prevention and treatment of depression. ❐

REFERENCES

1. Kupfer DJ, Foster FG. Interval between onset of sleep and rapid-eye-movement sleep as an indicator of depression. *Lancet*. 1972;2:684-686.
2. Mendelson WB, Gillin JC, Wyatt RD. *Human Sleep and its Disorders*. New York, NY: Plenum Press; 1977.
3. Casper RC, Redmond DE Jr, Katz MM, et al. Somatic symptoms in primary affective disorder: presence and relationship to the classification of depression. *Arch Gen Psychiatry*. 1985;42: 1098-1104.
4. Riemann D, Berger M, Voderholzer U. Sleep and depression: results from psychobiological studies: an overview. *Biol Psychol*. 2001;57:67-103.
5. Detre T, Himmelhoch J, Swartzburg M, Anderson CM, Byck R, Kupfer DJ. Hypersomnia and manic-depressive disease. *Am J Psychiatry*. 1972;128:123-125.
6. Thase ME, Himmelhoch JM, Mallinger AG, Jarrett DB, Kupfer DJ. Sleep EEG and DST findings in anergic bipolar depression. *Am J Psychiatry*. 1989;146:329-333.
7. Tam EM, Lam RW, Robertson HA, et al. Atypical depressive symptoms in seasonal and non-seasonal mood disorders. *J Affect Disord*. 1997;44:39-44.
8. Thase ME, Carpenter L, Kupfer DJ, Frank E. Clinical significance of reversed vegetative subtypes of major depression. *Psychopharmacol Bull*. 1991;27:17-22.
9. Kupfer DJ, Harrow M, Detre T. Sleep patterns and psychopathology. *Acta Psychiatr Scand*. 1969;45:75-89.
10. Kupfer DJ. REM latency: a psychobiologic marker for primary depressive disease. *Biol Psychiatry*. 1976;11:159-174.
11. Thase ME, Kupfer DJ, Spiker DG. Electroencephalographic sleep in secondary depression: a revisit. *Biol Psychiatry*. 1984;19: 805-814.
12. Berger M, Lund R, Bronisch T, von Zerssen D. REM latency in neurotic and endogenous depression and the cholinergic REM induction test. *Psychiatry Res*. 1983;10:113-123.
13. Riemann D, Fleckenstein P, Muller WE, Berger M. Are there biological markers for endogenous depression? In: Stefanis CN, Soldatos CR, Rabavilas AD, eds. *Psychiatry Today*. Proceedings of the VIII World Congress of Psychiatry; Athens, Greece. Amsterdam, Holland: Excerpta Medica; 1990, 280-284.
14. Riemann D, Hohagen F, Bahro M, Berger M. Sleep in depression: The influence of age, gender and diagnostic subtype on baseline sleep and the cholinergic REM induction test with RS 86. *Eur Arch Psychiatry Clin Neurosci*. 1994;243:279-290.
15. Rush AJ, Giles DE, Roffwarg HP, Parker CR. Sleep EEG and dexamethasone suppression test findings in outpatients with unipolar major depressive disorders. *Biol Psychiatry*. 1982;17:327-341.
16. Giles DE, Schlesser MA, Rush AJ, Orsulak PJ, Fulton CL, Roffwarg HP. Polysomnographic findings and dexamethasone nonsuppression in unipolar depression: a replication and extension. *Biol Psychiatry*. 1987;22:872-882.
17. Kerkhofs M, Kempenaers C, Linkowski P, der Maertelaer V, Mendlewicz J. Multivariate study of sleep EEG in depression. *Acta Psychiatr Scand*. 1988;77:463-468.
18. Kupfer DJ, Reynolds CF, Grochocinski VJ, Ulrich RF, McEeachran AB. Aspects of short REM latency in affective states: a revisit. *Psychiatry Res*. 1986;19:29-39.
19. Naylor MW, Shain BN, Shipley JE. REM latency in psychotically depressed adolescents. *Biol Psychiatry*. 1990;28:161-164.
20. Lauer CJ, Wiegand M, Krieg JC. All-night electroencephalographic sleep and cranial computed tomography in depression. *Eur Arch Psychiatry Clin Neurosci*. 1992;242:59-68.
21. Benca RM, Obermeyer WH, Thisted RA, et al. Sleep and psychiatric disorders: a meta-analysis. *Arch Gen Psychiatry*. 1992; 49:651-668.
22. Cartwright RD. Rapid eye movement sleep characteristics during and after mood-disturbing events. *Arch Gen Psychiatry*. 1983;40:197-201.
23. Buysse DJ, Frank E, Lowe KK, et al. Electroencephalographic sleep correlates of episode and vulnerability to recurrence in depression. *Biol Psychiatry*. 1997;41:406-418.
24. Knowles JB, Cairns J, McLean AW, et al. The sleep of remitted bipolar depressives: comparison with sex and age-matched controls. *Can J Psychiatry*. 1986;31:295-298.
25. Rush AJ, Erman MK, Giles DE, et al. Polysomnographic findings in recently drug-free and clinically remitted depressed patients. *Arch Gen Psychiatry*. 1986;43:878-884.
26. Giles DE, Etzel BA, Reynolds CF III, et al. Stability of polysomnographic parameters in unipolar depression: a cross-sectional report. *Biol Psychiatry*. 1989;25:807-810.
27. Giles DE, Jarrett RB, Roffwarg HP, et al. Reduced rapid eye movement latency: a predictor of recurrence in depression. *Neuropsychopharmacology*. 1987;1:33-39.
28. Kupfer DJ, Frank E, McEachran AB, et al. Delta sleep ratio: a biological correlate of early recurrence in unipolar affective disorder. *Arch Gen Psychiatry*. 1990;47:1100-1105.
29. Thase ME, Fasiczka AL, Berman SR, et al. Electroencephalographic sleep profiles before and after cognitive behaviour therapy of depression. *Arch Gen Psychiatry*. 1998;55:138-144.
30. Lauer CJ, Schreiber W, Holsboer F, et al. In quest of identifying vulnerability markers for psychiatric disorders by all-night polysomnography. *Arch Gen Psychiatry*. 1995;52:145-153.
31. Giles DE, Kupfer DJ, Rush AJ, et al. Controlled comparison of electrophysiological sleep in families of probands with unipolar depression. *Am J Psychiatry*. 1998;155:192-199.
32. Modell S, Ising M, Holsboer F, Lauer CJ. The Munich Vulnerability Study on Affective Disorders: premorbid polysomnographic profile of affected high-risk probands. *Biol Psychiatry*. 2005;58:694-699.
33. Garvey MJ, Mungas D, Tollefson GD. Hypersomnia in major depressive disorders. *J Affect Disord*. 1984;6:283-286.
34. Hawkins DR, Taub JM, Van de Castle RL. Extended sleep (hypersomnia) in young depressed patients. *Am J Psychiatry*. 1985; 142:905-910.
35. Thase ME. Depression, sleep, and antidepressants. *J Clin Psychiatry*. 1998;59(suppl 4):55-65.
36. Brunner DP, Krauchi K, Dijk DJ, Leonhardt G, Haug HJ, Wirz-Justice A. Sleep electroencephalogram in seasonal affective disorder and in control women: effects of midday light treatment and sleep deprivation. *Biol Psychiatry*. 1996;40:485-496.
37. Schwartz PJ, Rosenthal NE, Kajimura N, et al. Ultradian oscillations in cranial thermoregulation and electroencephalographic slow-wave activity during sleep are abnormal in humans with annual winter depression. *Brain Res*. 2000;866:152-167.
38. Miles LE, Dement WC. Sleep and aging. *Sleep*. 1980;3:119-121.
39. Bliwise DL. Sleep in normal aging and dementia. *Sleep*. 1993; 16:40-81.
40. Gillin JC, Duncan WC, Murphy DL, et al. Age related changes in sleep in depressed and normal subjects. *Psychiatry Res*. 1981; 4:73-78.
41. Lauer CJ, Riemann D, Wiegand M, Berger M. From early to late adulthood: changes in EEG sleep of depressed patients and healthy volunteers. *Biol Psychiatry*. 1991;29:979-993.
42. Armitage R, Hoffmann R, Fitch T, Trivedi M, Rush AJ. Slow-wave activity in NREM sleep: sex and age effects in depressed outpatients and healthy controls. *Psychiatry Res*. 2000;95:201-213.
43. Armitage R, Hoffmann R, Fitch T, Trivedi M, Rush AJ. Temporal characteristics of delta activity during NREM sleep in depressed outpatients and healthy adults: group and sex effects. *Sleep*. 2000;23:607-617.
44. Reynolds CF, Kupfer DJ, Thase ME, et al. Sleep, gender, and depression: an analysis of gender effects on the electroencephalo-

graphic sleep of 302 depressed outpatients. *Biol Psychiatry*. 1990; 28:673-684.
45. Thase ME, Kupfer DJ, Ulrich RF. Electroencephalographic sleep in psychotic depression: a revisit. *Arch Gen Psychiatry*. 1986;43:886-893.
46. Spiker DG, Coble P, Cofsky J, Foster FG, Kupfer DJ. EEG sleep and severity of depression. *Biol Psychiatry*. 1978;4:485-488.
47. Ford DE, Kamerow DB. Epidemiological study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. 1989;262: 1479-1484.
48. Eaton WW, Badawi M, Melton B. Prodromes and precursors: epidemiological data for primary prevention of disorders with slow onset. *Am J Psychiatry*. 1995;152:967-972.
49. Hohagen F, Rink K, Schramm E, Riemann D, Weyerer S, Berger M. Prevalence and treatment of insomnia in general practice—a longitudinal study. *Eur Arch Psychiatry Clin Neurosci*. 1993;242:325-336.
50. Schramm E, Hohagen F, Kappler C, Grasshoff U, Berger M. Mental comorbidity of chronic insomnia in general practice attenders using DSM-III-R. *Acta Psychiatr Scand*. 1995;91:10-17.
51. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry*. 1996;39:411-418.
52. Riemann D, Voderholzer U. Primary insomnia: a risk factor to develop depression. *J Affect Disord*. 2003;76:255-259.
53. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry*. 2003;160:1147-1156.
54. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The John Hopkins precursors study. *Am J Epidemiol*. 1997;146:105-114.
55. Tranter R, O'Donovan C, Chandarana P, et al. Prevalence and outcome of partial remission in depression. *J Psychiatry Neurosci*. 2002;27:241-247.
56. Thase ME, Simons AD, McGeary J, et al. Relapse after cognitive behaviour therapy of depression: potential implications for longer courses of treatments. *Am J Psychiatry*. 1992;149:1046-1052.
57. Judd LL, Akiskal HS, Maser JD, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch Gen Psychiatry*. 1998; 55:694-700.
58. Paykel ES. Remission and residual symptomatology in major depression. *Psychopathology*. 1998;31:5-14.
59. Judd LL, Akiskal HS, Zeller PJ, et al. Psychosocial disability during the long-term course of unipolar major depressive disorder. *Arch Gen Psychiatry*. 2000;57:375-380.
60. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry*. 1999;60:221-225.
61. Reynolds CF III, Frank E, Houch FE, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *Am J Psychiatry*. 1997;154:958-962.
62. Montgomery S, Roy D, Montgomery D. The prevention of recurrent suicidal acts. *Br J Clin Pharmacol*. 1983;15:183-188.
63. Choquet M, Kovess V, Poutignant N. Suicidal thoughts among adolescents: an intercultural approach. *Adolescence*. 1993;28: 649-659.
64. Gasquet I, Choquet M. Hospitalization in a pediatric ward of adolescent suicide attempters admitted to general hospitals. *J Adolesc Health*. 1994;15:416-422.
65. Hobson JA, McCarley RW, Wyzinski PW. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science*. 1975;189:55-58.
66. Borbély AA, Wirz-Justice A. Sleep, sleep deprivation and depression. *Hum Neurobiol*. 1982;1:205-210.
67. Guzmàn-Marin R, Alam MN, Szymuziak R, Drucker-Colin R, Gong H, McGinty D. Discharge modulation of rat dorsal raphe neurons during sleep and waking: effects of preoptic/basal forebrain warming. *Brain Res*. 2000;875:23-34.
68. Portas CM, Bjorvatn B, Ursin R. Serotonin and the sleep/wake cycle: special emphasis on microdialysis studies. *Progr Neurobiol*. 2000;60:13-35.
69. Steriade M, McCarley R. REM sleep as a biological rhythm. In: Steriade M & McCarley R, eds. *Brainstem control of wakefulness and sleep*. New York, NY: Plenum Press; 1990:363-393.
70. Gillin JC, Sutton L, Ruiz C, et al. The cholinergic rapid eye movement induction test with arecoline in depression. *Arch Gen Psychiatry*. 1991;48:264-270.
71. Hobson JA, Lydic R, Baghdoyan HA. Evolving concepts of sleep cycle generation: from brain centers to neuronal populations. *Behav Brain Sci*. 1986;9:371-448.
72. Riemann D, Berger M. Sleep, age, depression and the cholinergic REM induction test with RS 86. *Prog Neuropsychopharmacol Biol Psychiatry*. 1992;16:311-316.
73. Riemann D, Hohagen F, Gann H, et al. The REM sleep response to cholinergic stimulation: indicator of muscarinic supersensitivity in schizophrenia? *J Psychiatry Res*. 1994;28:195-210.
74. Sitaram N, Nurnberger JI, Gershon ES. Faster cholinergic REM sleep induction in euthymic patients with primary affective illness. *Science*. 1980;20:200-201.
75. Sitaram N, Nurnberg JI, Gershon ES, Gillin J. Cholinergic regulation of mood and REM sleep: potential model and marker of vulnerability to affective disorder. *Am J Psychiatry*. 1982;139: 571-576.
76. Borbély AA. A two process model of sleep regulation. *Hum Neurobiol*. 1982;1:195-204.
77. Sharpley AL, Cowen PJ. Effect of pharmacologic treatments on the sleep of depressed patients. *Biol Psychiatry*. 1995;37:85-98.
78. Gillin JC, Wyatt RF, Fram D, Snyder F. The relationship between changes in REM sleep and clinical improvement in depressed patients treated with amitriptyline. *Psychopharmacology*. 1978;59:267-272.
79. Hochli D, Riemann D, Zulley J, Berger M. Initial REM sleep suppression by clomipramine: a prognostic tool for treatment response in patients with a major depressive disorder. *Biol Psychiatry*. 1986;21:1217-1220.
80. Vogel GW. Evidence for REM sleep deprivation as the mechanism of action of antidepressant drugs. *Prog Neuropsychopharmacol Biol Psychiatry*. 1983;7:343-349.
81. Brunello N, Armitage R, Feinberg I, et al. Depression and sleep disorders: clinical relevance, economic burden and pharmacologic treatment. *Neuropsychobiology*. 2000;42:107-119.
82. Mendlewicz J, Dunbar GC, Hoffman G. Changes in sleep EEG architecture during the treatment of depressed patients with mianserin. *Acta Psychiatr Scand*. 1985;72:26-29.
83. Monti JM. Effect of a reversible monoamine oxidase-A inhibitor (moclobemide) on sleep of depressed patients. *Br J Psychiatry*. 1989;155:61-65.
84. Sharpley AL, Walsh AE, Cowen PJ. Nefazodone—a novel antidepressant—may increase REM sleep. *Biol Psychiatry*. 1992; 31:1070-1073.
85. Wilson S, Argyropoulos S. Antidepressants and sleep. A qualitative review of the literature. *Drugs*. 2005;65:927-947.
86. Rascati K. Drug utilization review of concomitant use of specific serotonin reuptake inhibitors or clomipramine with antianxiety/sleep medications. *Clin Ther*. 1995;17:786-790.
87. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. *Biol Psychiatry*. 1998;44:3-14.
89. Luthringer R, Toussaint M, Schaltenbrand N, et al. A double-blind, placebo-controlled evaluation of the effects of orally administered venlafaxine on sleep in patients with major depression. *Psychopharmacol Bull*. 1996;32:637-646.
90. Chalon S, Pereira A, Lainey E, et al. Comparative effects of duloxetine and desipramine on sleep EEG in healthy subjects. *Psychopharmacology*. 2005;4:357-365.
91. De Vane CL. Differential pharmacology of newer antidepressants. *J Clin Psychiatry*. 1998;59(suppl 20):85-93.
92. Winokur A, DeMartinis NA III, McNally DP, et al. Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. *J Clin Psychiatry*. 2003;64:1224-1229.
93. Mouret J, Lemoine P, Minuit MP, Benkelfat C, Renardet M. Effects of trazodone on the sleep of depressed subjects? A polysomnographic study. *Psychopharmacology*. 1988;95:S37-S43.
94. Jacobsen FM. Low-dose trazodone as a hypnotic in patients treated with MAOIs and other psychotropics: a pilot study. *J Clin Psychiatry*. 1990;51:298-302.
95. Zimmer B, Daly F, Benjamin L. More on combination antidepressant therapy. *Arch Gen Psychiatry*. 1984;41:527-528.
96. Armitage R, Yonkers K, Cole D, Rush AJ. A multicenter double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. *J Clin Psychopharmacol*. 1997;17:161-168.
97. Gillin JC, Rapaport M, Erman MK, Winokur A, Albala BJ. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. *J Clin Psychiatry*. 1997;58:185-192.
98. Quera Salva MA, Vanier B, Chapotot F, et al. Effect of agomelatine on sleep EEG in patients with major depressive disorder. *Eur Neuropsychopharmacol*. 2005;15(suppl 3):S435.
99. Guilleminault C. Efficacy of the new antidepressant agomelatine versus venlafaxine on subjective sleep of patients with major depressive disorder. *Eur Neuropsychopharmacol*. 2005;15 (suppl 3):S419.

SOMMEIL PERTURBÉ, UN SYMPTÔME MAJEUR DE LA DÉPRESSION

Les troubles subjectifs du sommeil, qu'ils soient typiques, comme l'insomnie d'endormissement, les réveils nocturnes fréquents, les réveils matinaux précoces, ou moins typiques, comme l'hypersomnie, sont fréquents dans la dépression majeure. Y sont également rattachées les variations polysomnographiques structurales, principalement l'augmentation de la « pression » de sommeil à mouvements oculaires rapides et la diminution du sommeil à ondes lentes. Certaines de ces modifications, sans qu'aucune ne soit spécifique de la dépression, persistent après la rémission et constituent ainsi un marqueur potentiel de vulnérabilité. Des données épidémiologiques suggèrent que les troubles du sommeil, au-delà de leur signification en tant que symptôme majeur de la dépression, seraient aussi un facteur de risque ou un symptôme prodromal d'un nouvel épisode dépressif ou encore un symptôme résiduel après un traitement efficace. La prise en charge de l'insomnie est donc essentielle dans la prévention et le traitement de la dépression. Les effets des antidépresseurs sur le sommeil subjectif et l'architecture du sommeil diffèrent à la fois entre les classes d'antidépresseurs et au sein d'une même classe. Les médecins doivent prendre ces effets en considération dans leur choix de l'antidépresseur le plus adapté pour un patient donné.

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Are sexual disorders core symptoms of depression?

by A. L. Montejo, Spain

Sexual dysfunction may be the commonest side effect of antidepressant therapy. The prime culprits—selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants—impair sexual function in up to 60% of patients, due to their serotonergic mechanism of action. Other antidepressants, however, with a different mechanism of action—bupropion, moclobemide, mirtazapine, and the recently introduced melatonergic antidepressant agomelatine—have many fewer sexual side effects. Quality of life is a major challenge for compliance with long-term treatment. Clinicians often underestimate sexual side effects and spontaneous reports by patients are few (14% to 24%). Brief, practical, and specific questionnaires can be helpful. Coping strategies include waiting for spontaneous remission, decreasing the dose, antidotes, and weekend drug holidays, but none are satisfactory for all patients. Probably the most effective method is to switch to a drug without sexual side effects. Primary prevention in sexually active patients begins with selecting a sexually nonincapacitating antidepressant. Clinicians should then systematically monitor the sexual effects of their treatment.

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Keywords: *antidepressant; management of sexual problems; sexual dysfunction; tolerability profile*

According to the National Health and Social Life Survey in a demographically representative cohort of US adults in 1992, sexual dysfunction (SD) is common, and more prevalent in women (43%) than men (31%).[1] In depressives, SD is a classic symptom. Depression is characterized by loss of interest and energy, low self-esteem, disturbed sleep, and anhedonia. A major consequence is a collapse in communication skills that impairs personal relationships. Many patients, due to lack of insight, take months or even years before seeking help. Such a scenario makes it difficult to lead a satisfactory sexual life. SD may actually be the problem that induces the patient and/or partner to seek help. SD is twice as common in depressed patients than in normal controls (50% versus 24%).[2]

A questionnaire relating to the month before diagnosis of major depression showed that 40% of men and 50% of women had decreased libido and sexual arousal; specifically orgasmic problems were less common (15% to 20%).

Because SD is such a frequent presenting complaint and may persist as a side effect of antidepressant treatment, it must be identified at diagnosis and monitored during therapy. The purpose of treating depression is to achieve complete remission without impairing quality of life. Treatment of a first episode may take several months, but may need to be maintained for years in recurrent depression and other chronic disease, such as anxiety or dysthymia. Long-term sexual side effects thus become a key aspect of tolerability, and hence treatment compliance. At worst, SD can be responsible for nonremission and recurrence.

Clinicians must take a careful sexual history before initiating antidepressant therapy. Sexual performance parameters should include libido, erectile function, vaginal lubrication, and ejaculation/orgasm. They should be periodically reviewed during follow-up. This will ensure early recognition of treatment-related SD.

SELECTED ABBREVIATIONS AND ACRONYMS

ASEX	Arizona Sexual Experiences Scale
CSFQ	Changes in Sexual Functioning Questionnaire
ED	erectile dysfunction
GABA	γ aminobutyric acid
GAD	generalized anxiety disorder
MAOI	monoamine oxidase inhibitor
PRSexDQ	Psychotropic-Related Sexual Dysfunction Questionnaire
SD	sexual dysfunction
SexFX	Sexual Effects (scale)
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor

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Antidepressant effects on sexual function and dysfunction

There are many causes of SD in major depression: the disease itself, the collapse in social and interpersonal relationships, and the medication, to name a few. The clinician's task is complicated by the fact that depression also makes it difficult for patients to communicate their complaints, in particular those concerning sexual function. As a result, this aspect is often underestimated.

Fortunately, however, SD has become increasingly recognized in recent years.[3-5] It is the commonest side effect of the antidepressants that increase serotonin levels: selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and clomipramine.[6,7] The resulting impact on quality of life leads to noncompliance with long-term treatments. SD is among the commonest side effects leading to dropout (50.8%).[8] The incidence of iatrogenic SD differs between antidepressants. It is more common with monoamine oxidase inhibitors (MAOIs), SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, and tricyclic antidepressants, in particular those with a high serotonin reuptake inhibitor profile, eg, clomipramine.[9,10] Bupropion,[11] mirtazapine, moclobemide,[12] and tianeptine are much less frequently involved, being nonserotonergic.

Antidepressants impair function across all sexual activity phases: desire, arousal, and orgasm/ejaculation. Among the less frequent changes, there are anecdotal reports of penile and clitoral anesthesia,[13,14] painful orgasm,[15] orgasm associated with yawning,[16,17] priapism associated with paroxetine[18] and trazodone,[19] increased libido,[20] spontaneous orgasm,[21] and decreased ejaculation volume.

The true incidence of such effects is unlikely to come to light unless explicitly elicited. Spontaneous report is uncommon, despite the potentially major impact of such side effects on treatment compliance. In a specific study, SD was volunteered by 14% of patients, but elicited in 58% by questionnaire.[22] Patients are not only embarrassed to mention SD, but also unhopeful of receiving help.[23] Reports on secondary SD have significantly increased since the 1980s, and comparison with placebo-treated patients and healthy volunteers has shown a close relationship between SD and antidepressant use. Clinicians should therefore be well prepared for managing such effects.

◆ *Mechanisms of antidepressant-related sexual dysfunction*

The normal sexual response includes a combination of neurogenic, psychogenic, vascular, and hormonal factors coordinated by higher centers *(Table I)* via multiple neurotransmitters, including dopamine, serotonin, norepinephrine, acetylcholine, γ-aminobutyric acid (GABA), oxytocin, arginine-vasopressin, angiotensin II, gonadotropin-releasing hormone, substance P, neuropeptide Y, and cholecystokinin-8.[24]

Hormones are particularly important: estrogen, testosterone, and progesterone in women, and testosterone in men. Dopamine enhances sexual function, while serotonin, via postsynaptic 5-HT_2 receptors, inhibits desire, and ejaculation/orgasm.[25,26] Noradrenergic influence is unclear, but appears to modulate the onset and maintenance of copulatory behavior in male rats.[27] Blockade of peripheral α-adrenergic and cholinergic receptors in the genitourinary tract impairs sexual function.[28] Potent anticholinergic agents and/or α_1-blockers (such as antidepressants and some antipsychotic agents) are strong inhibitors of sexual arousal.

Antidepressants may induce SD via an effect on nitric oxide.[29] Sildenafil, an effective treatment for erectile dysfunction (ED) of variable etiology, stimulates the action of nitric oxide. At the same time, many other drug classes are associated with SD, including cardiovascular agents (antihypertensives, digoxin), H_2 receptor antagonists, hormones, cytotoxics, and lipid-lowering agents, although such effects tend to be rarely reported to pharmacovigilance systems other than by manufacturers.[30] Adrenergic inhibition may mediate the effect of antihypertensives, eg, methyldopa, reserpine, clonidine, and propranolol, on erectile function and ejaculation.

- Increased serotonin activity
- Anticholinergic effect
- D_2 blockade
- Nitric oxide inhibition
- Endocrine changes: increased prolactin, decreased testosterone
- α_1-blockade (priapism)

Table I. Mechanisms involved in psychotropic-related sexual dysfunction.

◆ *The importance of specific questionnaires in eliciting sexual problems*

Several validated SD questionnaires have been developed in recent years *(Table II),* eg, the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ),[31] the Sex Effects (SexFX) scale,[32] the Changes in Sexual Functioning Questionnaire (CSFQ),[33] and the Arizona Sexual Experiences Scale (ASEX).[34]

The PRSexDQ has been used in several groups of depressed and schizophrenic patients on medication,[35] and in direct clinical interviews by the Span-

Scale Author/country	ASEX McGahuey USA	CSFQ Clayton USA	SexFX Kennedy Canada	PRSexDQ Montejo Spain
Questions	5	14	13	29
<10 minutes	yes	yes	yes	yes
Measures change	yes	yes	yes	yes
Intrusive	no	no	no	yes
Likert scale	yes	yes	yes	5 items
Specific drug–related	no	no	no	no
With interview	no	no	yes	no

Table II. Comparison of sexual dysfunction assessment instruments.
Abbreviations: ASEX, Arizona Sexual Experiences Scale; CSF-Q, Changes in Sexual Functioning Questionnaire; DISFSR, Derogatis Interview for Sexual Functioning Short Report; RSI, Rush Sexual Inventory; PRSexDQ, Psychotropic Related Sexual Dysfunction Questionnaire; SexFx, Sex Effects (scale).

ish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. It has shown satisfactory feasibility and good psychometric properties. It consists of 7 items assessing 5 dimensions of SD according to severity or frequency: loss of libido, delayed or absent orgasm/ejaculation, ED (men)/vaginal lubrication dysfunction (women), and patient acceptance of SD. In addition to individual item scores, it provides a summated scale score with items 3 to 7 ranging from 0 to 15 (severe SD).

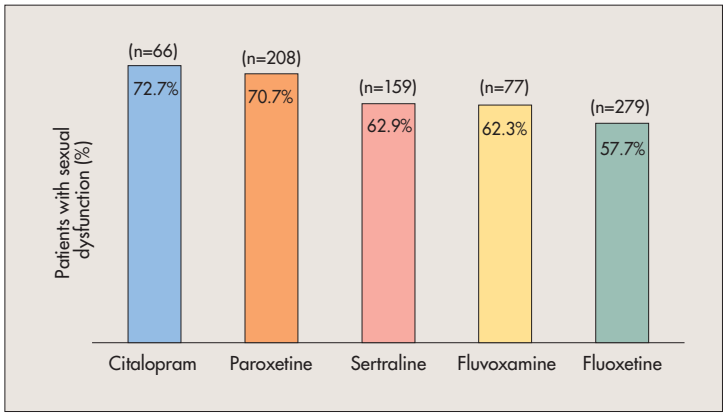

Figure 1. Prevalence of sexual dysfunction with selective serotonin reuptake inhibitors (SSRIs).

From reference 6: Montejo AL, Llorca G, Izquierdo JA, et al. Incidence of sexual dysfunction associated with different antidepressant agents. A prospective and multicenter study in 1022 patients. *J Clin Psychiatry.* 2001;62(suppl 3):10-21.[6] Copyright © 2001, Physicians Postgraduate Press, Inc.

The SexFX scale has been used in previous studies to compare sexual side effects associated with various antidepressants.[32] It is a brief scale developed to capture changes in the frequency of desire, arousal, and orgasm, which can be summed to provide a total SexFX score. Scale items are gender-specific where necessary. Two additional lines provide a global satisfaction score.

◆ *Frequency of antidepressant-related sexual dysfunction*

The PRSexDQ scale elicited a frequency of SD among antidepressant users that was significantly higher than volunteered SD (59.1% versus 24%) *(Figure 1)*. This confirmed studies reporting frequencies between 30% and 70%, and revealed the extent of a problem that would otherwise have gone undetected. A cross-sectional observational study using the CSFQ in 8312 US patients receiving antidepressant monotherapy revealed significant SD in 37%. Highest SD rates among SSRI and SNRI users belong to citalopram, paroxetine (the most potent SSRIs), and venlafaxine. Reports of male SD to the Committee on Safety of Medicines during the first 2 years of SSRI use in the UK were 10-fold higher for paroxetine than for remaining SSRIs. Meta-analysis also showed higher rates of SD and sedation with paroxetine over other SSRIs.[36] In our own patients, SD rates were slightly lower with fluoxetine than with other SSRIs. There is a clear relationship between serotonergic activity, lowered libido, and delay and/or absence of ejaculation/orgasm.

The reversible MAO-A inhibitor moclobemide has very little effect on sexual function, probably because it is dopaminergic and nonserotonergic. Bupropion, as a selective norepinephrine and dopamine reuptake inhibitor devoid of serotonergic activity, has similarly few effects, with SD rates no different from those on placebo in 6300 patients receiving a variety of newer antidepressants, including SSRIs and venlafaxine[37]; orgasmic dysfunction is less common than on SSRIs, and SD much less common than on venlafaxine.[38] Bupropion is similarly devoid of other common antidepressant-associated side effects, such as weight gain and sedation.

SSRIs may be the major culprits with regard to SD, but there are important differences between them. A prospective multicenter study in 1010 patients showed that decreased libido and delayed ejaculation/orgasm were the most frequent effects with SSRIs and venlafaxine *(Table III)*. ED was significantly less common than ejaculation problems, suggesting a different mechanism of action related not to serotonin, but rather to peripheral adrenergic and cholinergic pathways combined with other factors. The differences between paroxetine, citalopram, and venlafaxine were significant since ED rates approached 30% to 40%. Paroxetine was associated with significantly higher rates of ED or inadequate vaginal lubrication. This effect has been turned to advantage as a coadjuvant in the treatment of compulsive sexual behavior, premature ejaculation, and paraphilia.

SSRIs did not differ from venlafaxine in depressing libido, but paroxetine, for example, caused greater ED, possibly because it is a 5 to 160 times more potent cholinergic blocker than other SSRIs.

	Fluoxetine *N=279*	Paroxetine *N=208*	Fluvoxamine *N=77*	Sertraline *N=159*	Citalopram *N=66*	Venlafaxine *N=55*	Mirtazapine *N=49*
Decreased libido	50.2	63.9	48.1	54.7	62.1	60.0	20.4
Delayed orgasm	49.5	63.9	54.5	56.6	63.6	61.9	18.4
Anorgasmia	39.1	52.8	37.6	47.1	51.5	41.8	8.2
Erectile/ lubrication dysfunction	21.8	41.4*	20.8	28.9	34.8	40.0	14.2

Table III. Specific sexual side effect rates (%) with individual antidepressants in a multicenter study in 1010 evaluable patients. (*$P<0.05$ paroxetine versus other antidepressants.)

From reference 6: Montejo AL, Llorca G, Izquierdo JA, et al. Incidence of sexual dysfunction associated with different antidepressant agents. A prospective and multicenter study in 1022 patients. *J Clin Psychiatry.* 2001;62(suppl 3):10-21. Copyright © 2001, Physicians Postgraduate Press, Inc.

Good	Fair	Nil*
27.2%	34.5%	38.3%

*High dropout risk.

Table IV. Patient acceptance of sexual dysfunction.
From reference 42: Montejo AL. Beyond efficacy on the core symptoms of depression: sex and sleep benefits. *Eur Psychiatry.* 2007; 22(suppl 1):S92. Abstract. Copyright © 2007, Elsevier Masson SAS.

However, the recent discovery that it is a potent nitric oxide synthase inhibitor, both in vitro and in vivo, offers an alternative explanation.

With mirtazapine, SD is much less common (24.4%) and much less intense (delayed orgasm and milder anorgasmia) than with SSRIs and venlafaxine. However, ED is as severe as with the other drugs, due to the different mechanisms involved in erectile and orgasmic function. In several studies, SD improved markedly in patients switched to mirtazapine from other antidepressants. Mirtazapine has been reported to reverse SD when added to an SSRI. It also appears to improve SD in depressed men and women. However, this needs to be balanced against side effects such as weight gain and somnolence. A reported global improvement of 64.7% suggests that mirtazapine is a good therapeutic alternative in patients with severe SD, especially orgasmic problems, secondary to other drugs.[39]

The first case of SD reversal was recently described in a patient switched from one SSRI to another, escitalopram. The SNRI duloxetine appears to cause less SD than paroxetine or escitalopram.[40] However, there are too few controlled studies to conclude that SD is significantly less common with either escitalopram or duloxetine.

Agomelatine, a recent antidepressant with novel properties (a melatonin MT_1 and MT_2 receptor agonist, and a $5\text{-}HT_{2C}$ antagonist), preserves SD.[41-43] Agomelatine 50 mg/day was superior in both orgasm and preorgasm measures to venlafaxine XR 150 mg in remitted patients after 12 weeks, and was similar in antidepressant efficacy.[43] Agomelatine also caused significantly less SD than paroxetine (<10% versus >80%) in a sample of 90 healthy volunteers, and was indistinguishable in this regard from placebo.[44] Agomelatine resets circadian rhythms in depressed patients, significantly improves individual sleep phases and overall sleep quality, and does not cause daytime drowsiness.[45] Experience across a range of studies suggests that agomelatine offers a novel approach to the treatment of depression combining efficacy, even in severe disease, with an extremely favorable side-effect profile, with particular regard to sexual function.[45-48]

◆ *Effect of gender and age on sexual dysfunction in depression*

SD is slightly more common in men than women (62.4% versus 56.9%), but decreased libido, delayed orgasm, and anorgasmia are all more severe in women. Since women are generally more reluctant to report SD than men, it is especially important to monitor this aspect after initiating antidepressant treatment. Perhaps surprisingly, the older the patient, the less likely he or she is to tolerate SD. Length of treatment may be an important variable in this regard. The presence of SD could be secondary to a months-long history of impaired libido and ejaculation/orgasm.

◆ *Patient and/or partner acceptance of sexual dysfunction*

SD acceptance influences the rate of treatment dropout. We recently found SD well accepted by 27.2% of patients, accepted with reservations by 34.5%, and not accepted at all by 38.3%, in which case noncompliance rates were high *(Table IV).* Paroxetine was the least tolerated drug by patients with SD when compared with fluoxetine. Large-scale surveys have shown that between 41.7% and 50.8% of all withdrawals are due to side effects. Hence the importance of using alternative treatments to decrease the frequency and intensity of SD.

Management strategies

Several strategies are available for managing antidepressant-induced SD, including awaiting spontaneous remission, adjusting the dose, taking drug holidays, switching drugs, administering antidotes, and deploying nonpharmacologic strategies, although their efficacy remains mostly unknown or unproven *(Table V).*[49,50]

◆ Switch to bupropion and mirtazapine	C
◆ Switch to moclobemide, trazodone, reboxetine, maprotiline, escitalopram, tianeptine	NC
◆ Antidotes, buspirone, amantadine, selegiline, and *Ginkgo biloba* are NO better than placebo	C
◆ Sildenafil useful in erectile dysfunction	C
◆ Weekend holidays useful in anorgasmia	NC

Table V. Levels of evidence for management strategy in sexual dysfunction.
Abbreviations: C, controlled trials; NC, noncontrolled trials, small group or individual case reports.

Although spontaneous remission may occur after a while and for a while, at least 80% of patients with SD will have symptoms at 6 months. Differences between antidepressants in this regard are unknown, but durable spontaneous remission may prove more achievable with the newer dual-action agents such as SNRIs.

Tapered dose reduction is especially useful in patients who are also experiencing other side effects. However, it should only be attempted in good responders. Clinician and patient should be alert for any signs of relapse or discontinuation symptoms.

Drug holidays, in which patients skip treatment for a day or two, can be effective, but can also undermine treatment compliance. Even if instructed to take their treatment every day except at weekends, patients may still decide to skip other days as well. In addition, with short-acting SSRIs, drug holidays

can cause relapse or discontinuation symptoms. Replacing one SSRI with another may alleviate SD, but only in 10% of cases. Replacing SSRIs with drugs having a different mechanism of action, eg, bupropion[51] and mirtazapine,[52] appears more effective. Patients with GAD have also been successfully switched to the selective GABA reuptake inhibitor tiagabine with no further complaints of SD.[53] Agomelatine opens up interesting perspectives in this context, as it combines antidepressant efficacy and preservation of sexual function, making it particularly valuable in patients suffering from moderate-to-severe SD.

Antidotes may be an effective option for managing antidepressant-induced SD, but more data are required. Most of the available evidence derives from case reports, case series, and open-label trials. Antidotal therapy is claimed to alleviate SD and encourage compliance with the antidepressant regimen.[54] Antidotes commonly used in placebo-controlled trials have included drugs approved for treating ED, eg, sildenafil and tadalafil.[55]

Duloxetine and agomelatine are among the newer candidate antidotes. Sexual function was assessed using the ASEX in 4 double-blind placebo- and paroxetine-controlled trials of duloxetine in patients with major depression.[56] The incidence of treatment-emergent SD was significantly lower on duloxetine than on paroxetine, although both rates were higher than on placebo. In healthy volunteers, SD rates on agomelatine were similar to those on placebo and lower than on paroxetine. It appears a good alternative treatment for patients with moderate to severe SD on another antidepressant. A nonpharmacologic approach may also help. Simply talking may be enough in some patients, while others may benefit from sex therapy or trying different sexual techniques. Patients should also be warned against avoiding sexual activity, since maintaining a sex life helps to enhance improve sexual desire.

Conclusions

The incidence of antidepressant-related SD is underestimated. It occurs mainly with serotonergic agents such as SSRIs and venlafaxine. It is important because it impairs quality of life and increases the risk of noncompliance with a treatment that is often long-term and in some cases life-long. SD can only be effectively detected and managed during treatment if a detailed psychosexual history, including with the use of scales, has been taken before treatment. Alternative options are needed in patients in whom SD does not spontaneously remit and/or who find SD unacceptable. SD is not explicitly mentioned among the diagnostic criteria for Major Depressive Episode according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).* However, "markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly every day" could also be interpreted as loss in sexual interest.

This paper provides strong scientific evidence that sexual dysfunction should be considered as one of the core symptoms of depression, as is the case for depression, anhedonia, and disturbed sleep in depressed patients. New treatments that preserve sexual function could, in future, contribute to a better overall outcome of the treatment in terms of remission. In sexually active patients, the risk of SD must be a major consideration when selecting an antidepressant for long-term use. The best strategy is from the outset to use a drug with a known low SD potential. ❒

REFERENCES

1. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA.* 1999;281:537-544.

2. Casper RC, Redmond DE Jr, Katz MM, et al. Somatic symptoms in primary affective disorder: presence and relationship to the classification of depression. *Arch Gen Psychiatry.* 1985;42:1098-1104.

3. Bousoño M, Bascarán MT, Sáiz P, et al. [Sexual dysfunction as a key component in long-term antidepressant treatment]. *Psiquiatr Biol.* 1999;6(suppl 1):14-20.

4. Baldwin, D, Birtwistle J. Antidepressant drugs and sexual function: improving the recognition and management of sexual dysfunction in depressed patients. In: Briley M, Montgomery S, eds. *Antidepressant therapy at the dawn of the third millennium.* London, UK: Martin Dunitz; 1998, 231-255.

5. Werneke U, Northey S, Bhugra D. Antidepressants and sexual dysfunction. *Acta Psychiatr Scand.* 2006;114:384-397.

6. Montejo AL, Llorca G, Izquierdo JA, et al. Incidence of sexual dysfunction associated with different antidepressant agents. A prospective and multicenter study in 1022 patients. *J Clin Psychiatry.* 2001;62(suppl 3):10-21.

7. Montejo-González AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction. Fluoxetine, paroxetine, sertraline and fluvoxamine in a prospective, multicenter and descriptive clinical study of 344 patients. *J Sex Marital Ther.* 1997;23:176-184.

8. Kessler R. Advocacy groups: A cross-national comparison. New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association. NR 596. p. 228.

9. Laird LK. Sexual dysfunction on fluvoxamine therapy (letter). *J Clin Psychiatry.* 2000;61:62-63.

10. Kennedy SH, Eisfeld BS, Dickens SE, Bacchiochi JR, Bagby RM. Antidepressant-induced sexual dysfunction during treatment with moclobemide, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry.* 2000;61:276-281.

11. Settle EC, Stahl SM, Batey SR, Johnston JA, Ascher JA. Safety profile of sustained release bupropion in depression: results of three clinical trials. *Clin Ther.* 1999;21:454-463.

12. Philipp M, Kohnen R, Benkert O. A comparison study of moclobemide and doxepine in major depression with special reference to effects of sexual dysfunction. *Int Clin Psychopharmacol.* 1993;7:123-132.

13. Neill JR. Penile anesthesia associated with fluoxetine use (letter). *Am J Psychiatry.* 1991;148:1603.

14. King VL, Horovitz IR. Vaginal anesthesia associated with fluoxetine use (letter). *Am J Psychiatry.* 1993;150:984-985.

15. Aizenberg D, Zemishlany Z, Hermes H, et al. Painful ejaculation associated with antidepressants in four patients. *J Clin Psychiatry.* 1991;52:461-463.

16. McLean JD, Forsythe RG, Kapkin IA. Unusual side effects of clomipramine associated with yawning. *Can J Psychiatry.* 1983; 28:569-570.

17. Modell JG. Repeated observations of yawning, clitoral engorgement and orgasm associated with fluoxetine administration (letter). *J Clin Psychopharmacol.* 1989;9:63-65.

18. Ahmad S. Paroxetine induced priapism (letter). *Arch Intern Med.* 1995;155:645.

19. Chiang PH, Tsai EM, Chiang CP. The role of trazodone in the treatment of erectile dysfunction. *Kaohsiung J Med Sci.* 1994;10: 287-294.

20. Gartrell N. Increased libido in women receiving trazodone. *Am J Psychiatry.* 1986;143:781-782.

21. Labbate LA, Bupropion-SR-induced increased libido and spontaneous orgasm. *Can J Psychiatry.* 1998;43:644-645.

22. Montejo AL, Llorca G, Izquierdo JA, et al. [Sexual dysfunction due to SSRIs. Comparative analysis in 308 patients]. *Actas Luso Esp Neurol Psiquiatr.* 1996;24:311-321.

23. Marwick C. Survey says patients expect little physician help on sex. *JAMA*. 1999;281:2173-2174.
24. Baldwin D, Thomas S, Birtwistle J. Effects of antidepressant drugs on sexual function. *Int J Psychiatr Clin Pract*. 1997;1:47-58.
25. Mas M, Zahradnik MA, Martino V, Davidson JM. Stimulation of spinal serotonergic receptor facilitates seminal emission and suppresses penile erectile reflexes. *Brain Res*. 1985;342:639-648.
26. Sussman N. The potential benefits of serotonin receptor-specific agents. *J Clin Psychiatry*. 1994;55(suppl):45-51.
27. Caggiula AR, Shaw DH, Antelman M, Edwards DJ. Interactive effects of brain catecholamines and variations in sexual and nonsexual arousal on copulatory behavior of male rats. *Brain Res*. 1976;111:321-336.
28. Gitlin MJ. Psychotropic medications and their effects on sexual function: diagnosis, biology, and treatment approaches. *J Clin Psychiatry*. 1994;55:406-413.
29. Sussman N. SSRIs, yawning, orgasm-related events and nitric oxide: possible relationships. *Prim Psychiatr*. 1998;5:77-82.
30. Müller-Oerlinghaussen B, Ringel Y, Munter KH. The relevance of psychotropic-induced sexual dysfunction within de ADR voluntary reporting system in Germany. *Eur Psychiatr*. 1998;13(suppl 4):182s.
31. Montejo AL, Garcia M, Espada M, et al; Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. Psychometric characteristics of the psychotropic-related sexual dysfunction questionnaire. *Actas Esp Psiquiatr*. 2000;28:141-150.
32. Kennedy SH, Fulton KA, Bagby RM, Greene AL, Cohen NL, Rafi-Tari S. Sexual function during bupropion or paroxetine treatment of major depressive disorder. *Can J Psychiatry*. 2006; 51:234-242.
33. Clayton AH, McGarvey EL, Clavet GJ. The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. *Psychopharmacol Bull*. 1997;33:731-745.
34. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. *J Sex Marital Ther*. 2000;26:25-40.
35. Montejo AL, Rico-Villademoros F, Tafalla M. A 6-month prospective observational study on the effects of quetiapine on sexual functioning. *J Clin Psychopharmacol*. 2005;5:533-538.
36. Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs*. 1999; 57:507-533.
37. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry*. 2002;63:357-366.
38. Thase ME, Clayton AH, Haight BR, Thompson AH, Modell JG, Johnston JA. A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. *J Clin Psychopharmacol*. 2006;26:482-488.
39. Saiz-Ruiz J, Montes JM, Ibáñez A, et al. Assessment of sexual functioning in depressed patients treated with mirtazapine: a naturalistic 6-month study. *Hum Psychopharmacol*. 2005;20: 435-440.
40. Nierenberg AA, Greist JH, Mallinckrodt CH, et al. Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study. *Curr Med Res Opin*. 2007;23:401-416.
41. Rouillon F. Efficacy and tolerance profile of agomelatine and practical use in depressed patients. *Int Clin Psychopharmacol*. 2006;21(suppl 1):S31-S35.
42. Montgomery SA. Major depressive disorders: clinical efficacy and tolerability of agomelatine, a new melatonergic agonist. *Eur Neuropsychopharmacol*. 2006;16(suppl 5):S633-S638.
43. Kennedy SH. Favorable sexual profile of agomelatine in depressed patients. *Eur Neuropsychopharmacol*. 2006;16(suppl 4): S319. Abstract P.2.c.012.
44. Montejo AL. Beyond efficacy on the core symptoms of depression: sex and sleep benefits. *Eur Psychiatry*. 2007;22(suppl 1):S92. Abstract.
45. Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiatry*. 2007;68:1723-1732.
46. Lôo H, Hales A, D'haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT_{2C} antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int J Psychopharmacol*. 2002;17: 239-247.
47. Olié JP, Kasper S. Efficacy of agomelatine, a MT_1/MT_2 receptor agonist with 5-HT_{2C} antagonistic properties, in major depressive disorder. *Int J Neuropsychopharmacol*. 2007;10:661-673.
48. Montgomery SA, Kasper S. Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. *Int J Psychopharmacol*. 2007;22:283-291.
49. Clayton AH, Montejo AL. Major depressive disorder, antidepressants, and sexual dysfunction. *J Clin Psychiatry*. 2006;67 (suppl 6):33-37.
50. Taylor MJ. Strategies for managing antidepressant-induced sexual dysfunction: a review. *Curr Psychiatry Rep*. 2006;8:431-436.
51. Clayton AH, Warnock JK, Kornstein SG, et al. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry*. 2004;65:62-67.
52. Koutouvidis N, Pratikakis M, Fotiadou A. The use of mirtazapine in a group of 11 patients following poor compliance to selective serotonin reuptake inhibitor treatment due to sexual dysfunction. *Int Clin Psychopharmacol*. 1999;14:253-255.
53. Schwartz TL, Nasra GS, Ashton AK, et al. An open-label study to evaluate switching from an SSRI or SNRI to tiagabine to alleviate antidepressant-induced sexual dysfunction in generalized anxiety disorder. *Ann Clin Psychiatry*. 2007;19:25-30.
54. Nurnberg HG, Hensley PL, Gelenberg AJ, et al. Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. *JAMA*. 2003;289:56-64.
55. Segraves RT, Lee J, Stevenson R, Walker DJ, Wang WC, Dickson RA. Tadalafil for treatment of erectile dysfunction in men on antidepressants. *J Clin Psychopharmacol*. 2007;27:62-66.
56. Delgado PL, Brannan SK, Mallinckrodt CH, et al. Sexual functioning assessed in 4 double-blind placebo- and paroxetine-controlled trials of duloxetine for major depressive disorder. *J Clin Psychiatry*. 2005;66:686-692.

LES TROUBLES SEXUELS SONT-ILS DES SYMPTÔMES MAJEURS DE LA DÉPRESSION ?

Les troubles sexuels semblent être l'effet indésirable le plus fréquent du traitement antidépresseur. Les premiers coupables, les inhibiteurs sélectifs de la recapture de la sérotonine, les inhibiteurs de la recapture de la sérotonine et de la noradrénaline et les antidépresseurs tricycliques, altèrent la fonction sexuelle de près de 60 % des patients en raison de leur mécanisme d'action sérotoninergique. D'autres antidépresseurs, tels que le bupropion, le moclobémide, la mirtazapine et un nouvel antidépresseur mélatoninergique, l'agomélatine, ont cependant beaucoup moins d'effets sexuels indésirables de par leur mode d'action différent. La qualité de vie est le principal critère d'observance d'un traitement au long cours. Les effets sexuels indésirables sont souvent sous-estimés par les médecins et rarement évoqués spontanément par les patients (14 % à 24 %). Des questionnaires brefs, pratiques et spécifiques peuvent être utiles. Aucune des stratégies d'ajustement n'est satisfaisante pour la totalité des patients, qu'il s'agisse de l'attente d'une rémission spontanée, de la diminution de posologie, d'antidotes et de fenêtre thérapeutique du week-end. La méthode la plus efficace est probablement celle du changement de classe thérapeutique vers un médicament sans effets secondaires sexuels. Outre la prévention primaire pour les patients sexuellement actifs, qui passe par le choix d'un antidépresseur n'inhibant pas la fonction sexuelle, le médecin se doit d'évaluer systématiquement les effets sexuels des traitements prescrits.

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Chronobiology of the core symptoms of depression

by A. Germain and E. Frank, USA

Depression is characterized by disturbances in multiple physiological, neuroendocrine, neurobiological, behavioral, and social rhythms. A number of depressive symptoms vary in severity over a 24-hour period. Diurnal mood variations and sleep disturbances are the most commonly observed circadian disturbances in depressed patients. Circadian disturbances affect treatment response and clinical outcome. Similarly, regularizing and stabilizing behavioral and social rhythms in patients with mood disorders directly benefits mood symptoms and clinical outcome. We briefly describe some of the ultradian and circadian disturbances reported in major depression before discussing the relationship between sleep disturbance and the course and outcome of depression. We then present an alternative to the pharmacotherapeutic approach, namely social rhythm therapy, which is designed to regularize social rhythms in patients with mood disorders. Recognizing circadian variations in symptoms and aiming to regularize circadian and sleep disturbance may enhance treatment outcome in depression.

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Keywords: *chronobiology; circadian rhythm; depression; mood symptoms*

All species exhibit marked endogenous variations in several physiological and behavioral rhythms. Rhythms that approximate the 24-hour light-dark cycle are termed circadian (from the Latin *circa diem,* "about a day"), whereas those that are shorter or longer than the 24-hour cycle are termed ultradian and infradian, respectively. These cyclic processes are endogenously generated, maintained, and regularized. Synchronization of multiple endogenous processes enhances survival. A central homeostatic pacemaker, the suprachiasmatic nucleus (SCN) of the hypothalamus, orchestrates the multiple oscillator systems. To further enhance survival, the pacemaker is adaptable. It can be entrained to respond directly or indirectly to external time givers, or zeitgebers. Stimuli from the environment (light/dark), behavior (meals, sleep), and social stimuli entrain the circadian pacemaker to the 24-hour cycle. In humans, circadian variations characterize multiple physiological and psychological functions, including core body temperature, endocrine and autonomic functions, sleep, mood, alertness, and cognitive performance.[1-4] Core body temperature peaks during the day, and drops during the night. Melatonin levels peak during the night, and are lowest during the day. Cortisol levels reach a low at bedtime and rise again in the morning. Thyroid stimulating hormone peaks prior to sleep onset, wanes during the night, and rises again during the day.[4]

Sleep and wakefulness are the most obvious manifestations of the mammalian circadian system. The drive to sleep is determined by two processes, one homeostatic (process S), and the other circadian (process C).[5,6] Process S increases sleep propensity with increasing duration of prior wakefulness. Process C is a SCN-dependent circadian mechanism,[5,6] which integrates and reinforces endogenous and exogenous zeitgebers to enhance the maintenance of wakefulness during the circadian day, and to enhance the maintenance of sleep during the night.

Healthy subjects typically report mood deterioration in the evening compared with the morning.[7,8] Mood variation across the 24-hour cycle depends on the interaction between circadian phase and the duration of prior wakefulness.[1] Mood, alertness, and cognitive performance decline during the day, and are worst during the night.[4,9]

SELECTED ABBREVIATIONS AND ACRONYMS

IPSRT	interpersonal therapy social rhythm therapy
REM	rapid eye movement
SCN	suprachiasmatic nucleus
SRM	Social Rhythm Metric

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Circadian disturbances have been reported in multiple physiological systems in patients with major depression. Increased mean core temperature and decreased period amplitude are well documented.[10] Circadian oscillations in plasma cortisol and norepinephrine occur earlier in the 24-hour period, or are phase-advanced, compared with healthy subjects;[11] 24-hour cortisol secretion is more variable[12] and less closely related to social zeitgebers.[13] Abnormal levels and patterns of melatonin secretion have also been observed in some,[14] but not all studies.[15] Sleep disruption is a particularly well-documented circadian disturbance in depression, as discussed in more detail below.

Circadian disturbances in depression may relate to impaired generation of circadian rhythms, desynchronization of multiple circadian rhythms, and blunted responsiveness of the circadian system to entrainment cues, or to reduced exposure to, frequency of, these entrainment cues due to the reduced activity levels, anhedonia, and social isolation that characterize depressive episodes. In sum, complex disturbances in multiple circadian mechanisms may account for the heterogeneity of symptoms in mood disorders and their diurnal variation. For instance, reduced amplitude of 24-hour cortisol levels is apparent in nonpsychotic depressed patients, but not in patients with the psychotic subtype of depression.[16]

Diurnal variations of depressive symptoms

Some depressive symptoms show considerable diurnal disturbance in major depression. Many patients with nonseasonal depression show a regular daily pattern of symptoms, usually more severe in the morning, whereas healthy subjects typically report mood deterioration in the evening compared with the morning. Diurnal mood variation (with improved mood in the evening) in depressed patients predicts an antidepressant response to sleep deprivation.[17-19] A minority of depressed patients show the opposite pattern (reversed diurnal variation[20]), with mood deterioration in the evening relative to the morning.

A recent study compared the neuroanatomical correlates of diurnal mood variation between depressed and healthy subjects.[21] Depressed patients exhibited different patterns of variation in regional brain glucose metabolism across times of day compared with healthy subjects. Specifically, during the morning, they showed more activity in brain regions involved in affect production. In the evening, when mood ratings improved in depressed subjects and worsened in healthy subjects, depressed patients showed increased activity in brain regions involved in affect regulation. These findings suggest that evening mood improvement in depressed patients may be related to normalization of the mechanisms underlying affect production and regulation.[22,23]

Among circadian disturbances associated with depression, those affecting sleep are by far the most common and well documented. Up to 90% of depressed patients report sleep onset insomnia, sleep maintenance insomnia, and early morning awakenings,[24] while a minority (6% to 29%) report hypersomnia.[25] Objective sleep measures are also disturbed.[26] The latency between sleep onset and the first episode of rapid eye movement (REM) sleep is typically shortened. Depressed patients exhibit longer REM sleep, more eye movements during REM sleep, and shorter slow-wave sleep than healthy subjects.[24] Depressed patients also differ in alertness over the 24-hour cycle compared with normals. Sustained alertness across the 24-hour cycle in depressed patients may relate to heightened neuronal activity in the brainstem and hypothalamic regions involved in maintaining daytime wakefulness. In healthy subjects, brain glucose metabolism is increased in the brainstem and hypothalamic regions involved in maintaining wakefulness in the evening relative to the morning. This may reflect an increased circadian drive to remain alert as sleep propensity increases in the evening.[27]

Diurnal patterns of motor activity tend to differ between patients with major depression and healthy subjects.[28] Continuous activity measurement using actigraphs (wristwatch-like devices) that detect and store information on wrist movement have consistently shown greater between-patient variability and reduced activity levels across the 24-hour cycle in depressed patients.[29,30] Speech pause time is also increased.[31,32] Differences in patterns of reaction time and cognitive performance have also been reported. Specifically, depressed patients are slower in decision time and motor performance in morning testing, but not evening testing.[33-35]

While some evidence suggests that diurnal variation in depressive symptoms parallels diurnal variation in neurobiological and neuroendocrine activity, the specific underlying mechanisms remain largely unelucidated. Recent advances in molecular biology suggest that polymorphisms in circadian (or clock) genes constitute a critical mechanism by which circadian and sleep disturbances predispose to depressive illness[33] and underlie diurnal symptom variation. Additionally, the role of disrupted social rhythms as mediators of the relationships between diurnal symptom variation and physiological circadian disturbances remains unknown. Several studies have now shown that social rhythms are disrupted and less regular in patients with mood disorders and individuals undergoing stressful life events.[36-40] Disrupted social rhythms may be directly responsible for diurnal depressive symptom variation. The association between increased regularity of social rhythms and reduced depression severity[41-43] suggests that irregular social rhythms may mediate the relationship between diurnal symptom variation and physiological circadian disturbances.

Relationship between sleep disturbances and depression

There is clinical and epidemiological evidence that sleep disturbance in depression is a risk factor for poor clinical outcomes. Insomnia complaints precede the onset and recurrence of depression[44] in up to 40% of cases.[45] The risk of developing major de-

pression is significantly increased in individuals complaining of insomnia.[46-48] Insomnia and hypersomnia complaints are associated with increased suicidality.[49] Furthermore, sleep disturbances in depression predict treatment outcome. Specifically, poor sleep quality predicts poor response to non-pharmacological treatments.[50,51] Persistent REM sleep abnormalities and poor sleep quality post-psychotherapy are associated with nonresponse[50] and recurrence.[51] Subjective reports of better sleep quality post-treatment are associated with less recurrent depression. Together, these observations suggest a critical role for sleep disturbances in the pathophysiology of depression.

Modification of social rhythms as a treatment of depression

Disruption of the physiological indices of circadian rhythms is associated with mood symptoms in depression. Disruption of social rhythms is also paralleled by changes in physiological rhythms, and may directly contribute to depressive episodes. Social rhythms refer to nonphotic environmental stimuli, or social zeitgebers, such as social interaction, meals, and other routines that entrain the central and peripheral pacemakers. Depression clearly disrupts daily occupational and social routines. Similarly, changes in appetite affect the regularity and frequency of meals. In vulnerable individuals, social rhythm disruption may trigger mood episodes by reducing exposure to, and the frequency of, social zeitgebers. Life events that directly change daytime routines, eg, retirement and bereavement,[42,52] birth of a child, jet lag, and shift work, are especially likely to trigger a depressive episode.[38,53]

Frank and colleagues[36,54] developed the interpersonal and social rhythm therapy (IPSRT) intervention program to restore and consolidate social rhythm regularity as a protective strategy against relapse. Their rationale was that mood disorders result from complex interaction between genetic vulnerability, psychosocial stressors, and circadian rhythmicity that can have positive or negative affects on adherence to pharmacotherapy.

The first step in IPSRT is to identify the disrupted and/or irregular social rhythms (eg, sleep-wake schedules, meal times, exercise times, and irregular occupational schedules such as shift work and unemployment). A validated instrument for measuring social rhythm regularity is the Social Rhythm Metric (SRM, *Figure 1*),[55] a self-reported measure completed over a predetermined period (14 days to 1 month), on which patients prospectively log the timing of different social rhythm components (time out of bed, time in bed, meal times, time of first social contact, time of exercise sessions, time of first outdoor light exposure, and start time of occupational activities). The SRM also includes items to specify whether the different components are performed alone, or in the presence of another person (whether actively involved or not).

Based on the data derived from this first step, stabilization goals can then be identified and implemented. Typical goals include establishing regular bed, wake, and meal times, switching to a more regular work schedule, and incorporating a regular daily exercise session. Strategies should be individually tailored. Reinforcement by regular activity is a critical element of IPSRT. Consolidation is provided by devising specific protective strategies to minimize dysregulation of social rhythms by expected predictable and unexpected stressors.[36,56]

IPSRT has been most widely used in bipolar patients, in whom it reduces the risk of recurrence; emerging evidence suggests that it also effectively regularizes social rhythms, accelerates remission in depressed patients, and lowers relapse rates compared with intensive pharmacotherapy.[57] These observations warrant more direct investigation of IPTSRT as an adjunctive or stand-alone treatment in major depression.

Please fill this out at the end of the day

Day of week:

ACTIVITY	Check if did not do	TIME: Clock time	TIME: Check A.M.	TIME: Check P.M.	Check if alone	PEOPLE (1 = just present, 2 = actively involved): Spouse/partner	Children	Other family members	Other person(s)
Sample activity (for reference only)		6:20	✓			2			1
Out of bed									
First contact (in person or by phone) with another person									
Have morning beverage									
Have breakfast									
Go outside for the first time									
Start work, school, housework, volunteer activities, child or family care									
Have lunch									
Take an afternoon nap									
Have dinner									
Physical exercise									
Have an evening snack/drink									
Watch evening TV news program									
Watch another TV program									
Activity A									
Activity B									
Return home (last time)									
Go to bed									

Figure 1. The Social Rhythm Metric.

Modified from reference 55: Monk TH, Flaherty JF, Frank E, Hoskinson K, Kupfer DJ. The Social Rhythm Metric. An instrument to quantify the daily rhythms of life. *J Nerv Ment Dis.* 1990;178:120-126.

Conclusion

Disruption of circadian and ultradian physiological and social rhythms characterizes depression, and may directly contribute to its pathophysiology.

Mood variation and sleep disturbance are robust manifestations of circadian disruption in depressed patients, and both predict treatment response and outcomes. Circadian disturbances in social and sleep rhythms are risks for mood disorders that can be attenuated by behavioral interventions that target the regularization and consolidation of stable rhythms. Innovative pharmacological approaches that can normalize circadian rhythms in depression can also offer promising clinical perspectives.[58,59] Further investigation of the molecular, physiological, and social mechanisms that contribute to the relationship between circadian disturbances and mood disorders is required to guide the development of new and effective strategies that directly normalize the circadian abnormalities underlying depression and hence enhance treatment outcome. ❐

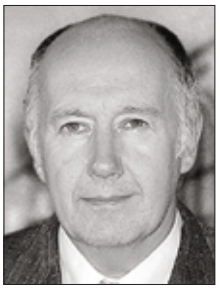
REFERENCES

1. Boivin DB, Czeisler CA, Dijk DJ, et al. Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. *Arch Gen Psychiatry*. 1997;54:145-152.
2. Adan A, Sanchez-Turer M. Gender differences in diurnal variations of subjective activation and mood. *Chronobiol Int*. 2001; 18:491-502.
3. Monk TH, Buysse DJ, Carrier J, Billy BD, Rose LR. Effects of afternoon "siesta" naps on sleep, alertness, performance and circadian rhythms in the elderly. *Sleep*. 2001;24:680-687.
4. Czeisler CA, Buxton OM, Khalsa SB. The human circadian timing system and sleep-wake regulation. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine,* 4th ed. Philadelphia, Pa: Elsevier/Saunders; 2005.
5. Achermann P, Borbely AA. Mathematical models of sleep regulation. *Front Biosci*. 2003;8:S683-S693.
6. Borbely AA, Baumann F, Brandeis D, Strauch I, Lehmann D. Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalogr Clin Neurophysiol*. 1981;51:483-495.
7. Gordijn MC, Beersma DG, Bouhuys AL, Reinink E, Van den Hoofdakker RH. A longitudinal study of diurnal mood variation in depression; characteristics and significance. *J Affect Disord*. 1994;31:261-273.
8. Goetze U, Tolle R. [Antidepressive effect of partial sleep deprivation during the first half of the night]. *Psychiatr Clin*. 1981;14: 129-149.
9. Monk TH, Buysse DJ, Reynolds CF, et al. Circadian rhythms in human performance and mood under constant conditions. *J Sleep Res*. 1997;6:9-18.
10. Souetre E, Salvata E, Belugou J, et al. Circadian rhythms in depression and recovery: Evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res*. 1989;28: 263-278.
11. Koenigsberg HW, Teicher MH, Mitropoulou V, et al. 24-Hour monitoring of plasma norepinephrine, MHPG, cortisol, growth hormone and prolactin in depression. *J Psychiatr Res*. 2004;38: 503-511.
12. Peeters F, Nicholson NA, Berkhof J. Cortisol responses to daily events in major depressive disorder. *Psychosom Med*. 2003; 65:836-841.
13. Stetler C, Dickerson SS, Miller GE. Uncoupling of social zeitgebers and diurnal cortisol secretion in clinical depression. *Psychoneuroendocrinology*. 2004;29:1250-1259.
14. Claustrat B, Chazot G, Brun J, Jordan D, Sassolas G. A chronobiological study of melatonin and cortisol secretion in depressed subjects: plasma melatonin, a biochemical marker in major depression. *Biol Psychiatry*. 1984;19:1215-1228.
15. Thompson C, Franey C, Arendt J, Checkley SA. A comparison of melatonin secretion in depressed patients and normal subjects. *Br J Psychiatry*. 1988;152:260-265.
16. Posener JA, DeBattista C, Williams GH, Chmura KH, Kalehzan BM, Schatzberg AF. 24-Hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Arch Gen Psychiatry*. 2000;57:755-760.
17. Haug HJ. Prediction of sleep deprivation outcome by diurnal variation of mood. *Biol Psychiatry*. 1992;31:271-278.
18. Reinink E, Bouhuys N, Wirz-Justice A, Van den Hoofdakker HR. Prediction of the antidepressant response to total sleep deprivation by diurnal variation of mood. *Psychiatry Res*. 1990;32: 113-124.
19. Reinink E, Bouhuys AL, Gordijn MC, Van den Hoofdakker RH. Prediction of the antidepressant response to total sleep deprivation of depressed patients: longitudinal versus single day assessment of diurnal mood variation. *Biol Psychiatry*. 1993;34:471-481.
20. Joyce PR, Porter RJ, Mulder RT, et al. Reversed diurnal variation in depression: associations with a differential antidepressant response, tryptophan:large neutral amino acid ratio and serotonin transporter polymorphisms. *Psychol Med*. 2005;35:511-517.
21. Germain A, Nofzinger EA, Meltzer CC, et al. Diurnal variation in regional brain glucose metabolism in depression. *Biol Psychiatry*. 2007;62:438-445.
22. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry*. 2003;54:504-514.
23. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry*. 2003; 54:515-528.
24. Tsuno N, Besset A, Ritchie K. Sleep and depression. *J Clin Psychiatry*. 2005;66:1254-1269.
25. Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints and depression in an aging cohort: a prospective perspective. *Am J Psychiatry*. 2000;157:81-88.
26. Riemann D, Berger M, Voderholzer U. Sleep and depression–results from psychobiological studies: an overview. *Biol Psychol*. 2001;57:67-103.
27. Buysse DJ, Nofzinger EA, Germain A, et al. Regional brain glucose metabolism during morning and evening wakefulness in humans: preliminary findings. *Sleep*. 2004;27:1245-1254.
28. Sobin C, Sackeim HA. Psychomotor symptoms of depression. *Am J Psychiatry*. 1997;154:4-17.
29. Wehr TA, Goodwin FK. Desynchronization of circadian rhythms as a possible source of manic-depressive cycles. P*sychopharmacol Bull*. 1980;16:19-20.
30. Wolff EA, Putnam FW, Post RM. Motor activity and affective illness. *Arch Gen Psychiatry*. 1985;42:288-294.
31. Greden JF, Carroll BJ. Psychomotor function in affective disorders: an overview of new monitoring techniques. *Am J Psychiatry*. 1981;11:1441-1448.
32. Szabadi E, Bradshaw CM, Besson JA. Elongation of pause-time in speech: a simple, objective measure of motor retardation in depression. *Br J Psychiatry*. 1976;129:592-597.
33. Bunney WE, Bunney BG. Molecular clock genes in man and lower animals: possible implications for circadian abnormalities in depression. *Neuropsychopharmacology*. 2000;22:335-345.
34. Moffoot AP, O'Carroll RE, Bennie J, et al. Diurnal variation of mood and neuropsychological function in major depression with melancholia. *J Affect Disord*. 1994; 32:257-269.
35. Porterfield T, Cook M, Deary IJ, Ebmeier KP. Neuropsychological function and diurnal variation in depression. *J Clin Exp Neuropsychol*. 1997;19:906-913.
36. Frank E, Kupfer DJ, Ehlers CL, et al. Interpersonal and social rhythm therapy for bipolar disorder: integrating interpersonal and behavioral approaches. *Behav Ther*. 1995;17:144-149.
37. Frank E, Hlastala S, Ritenour A, et al. Inducing lifestyle regularity in recovering bipolar disorder patients: results from the maintenance therapies in bipolar disorder protocol. *Biol Psychiatry*. 1997;41:1165-1173.
38. Malkoff-Schwartz S, Frank E, Anderson B, et al. Stressful life events and social rhythm disruption in the onset of manic and depressive bipolar episodes: a preliminary investigation. *Arch Gen Psychiatry*. 1998;55:702-707.
39. Prigerson HG, Reynolds CF, Frank E, Kupfer DJ, George CJ, Houck PR. Stressful life events, social rhythms, and depressive symptoms among the elderly: an examination of hypothesized causal linkages. *Psychiatry Res*. 1994;51:33-49.
40. Shear MK, Randall J, Monk TH, et al. Social rhythm in anxiety disorder patients. *Anxiety*. 1994;1:90-95.
41. Monk TH, Petrie SR, Hayes AJ, Kupfer DJ. Regularity of daily life in relation to personality, age, gender, sleep quality and circadian rhythms. *J Sleep Res*. 1994;3:196-205.
42. Brown LF, Reynolds CF, Monk TH, et al. Social rhythm stability following late-life spousal bereavement: ssociations with depression and sleep impairment. *Psychiatry Res*. 1996;62:161-169.
43. Szuba MP, Yager A, Guze BH, Allen EM, Baxter JR. Disruption of social circadian rhythms in major depression: a preliminary report. *Psychiatry Res*. 1992;42:221-230.
44. Riemann D, Voderholzer U. Primary insomnia: a risk factor to develop depression? *J Affect Disord*. 2003;76:255-259.
45. Ohayon MM, Roth T. Place of chronic insomnia in the course

of depressive and anxiety disorders. *J Psychiatr Res.* 2003;37:9-15.
46. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry.* 1996;39:411-418.
47. Livingston G, Blizard B, Mann A. Does sleep disturbance predict depression in elderly people? A study in inner London. *Br J Gen Pract.* 1993;43:445-448.
48. Vollrath M, Wicki W, Angst J. The Zurich study. VIII. Insomnia: association with depression, anxiety, somatic syndromes, and course of insomnia. *Eur Arch Psychiatry Neurol Sci.* 1989;239:113-124.
49. Agargun MY, Kara H, Solmaz M. Sleep disturbances and suicidal behavior in patients with major depression. *J Clin Psychiatry.* 1997;58:249-251.
50. Buysse DJ, Tu XM, Cherry CR, Begley AE, et al. Pretreatment REM sleep and subjective sleep quality distinguish depressed psychotherapy remitters and nonremitters. *Biol Psychiatry.* 1999;45:205-213.
51. Buysse DJ, Frank E, Lowe KK, Cherry CR, Kupfer DJ. Electroencephalographic sleep correlates of episode and vulnerability to recurrence in depression. *Biol Psychiatry.* 1997;41:406-418.
52. Monk TH, Houck PR, Shear MK. The daily life of complicated grief patients: what gets missed, what gets added? *Death Stud.* 2006;30:77-85.
53. Malkoff-Schwartz S, Frank E, Anderson BP, et al. Social rhythm disruption and stressful life events in the onset of bipolar and unipolar episodes. *Psychol Med.* 2000;30:1005-1016.
54. Frank E. *Treating Bipolar Disorder: A Clinician's Guide to Interpersonal and Social Rhythm Therapy.* New York, NY: Guilford Press; 2005.
55. Monk TH, Flaherty JF, Frank E, Hoskinson K, Kupfer DJ. The Social Rhythm Metric: an instrument to quantify the daily rhythms of life. *J Nerv Ment Dis.* 1990;178:120-126.
56. Frank E, Swartz HA, Kupfer DJ. Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. *Biol Psychiatry.* 2000;48:593-604.
57. Frank E, Kupfer DJ, Thase ME, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch Gen Psychiatry.* 2005;62:996-1004.
58. Lader M. Limitations of current medical treatments for depression: disturbed circadian rhythms as a possible therapeutic goal. *Eur Neuropsychopharmacol.* 2006;17:743-755.
59. Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur Neuropsychopharmacol.* 2006;16:93-100.

CHRONOBIOLOGIE DES SYMPTÔMES MAJEURS DE LA DÉPRESSION

La dépression est caractérisée par des troubles affectant de nombreux rythmes physiologiques, neuroendocriniens, neurobiologiques, comportementaux et sociaux. Un certain nombre de symptômes dépressifs présentent des variations de la sévérité au cours du nycthémère. Les troubles circadiens les plus couramment observés chez les patients déprimés sont des variations diurnes de l'humeur et des troubles du sommeil. Ces perturbations compromettent l'évolution clinique et la réponse au traitement. À l'inverse, la régularisation et la stabilisation des rythmes sociaux et comportementaux des patients ayant des troubles de l'humeur améliorent directement l'évolution clinique et les symptômes thymiques. Cet article décrit brièvement certains troubles ultradiens ou circadiens observés dans la dépression majeure avant d'étudier les liens entre les troubles du sommeil et l'évolution et l'issue de la dépression. Une alternative au traitement pharmacologique, basée sur la régularisation des rythmes sociaux chez les patients dysthymiques (social rhythm therapy), est décrite. La reconnaissance des variations circadiennes des symptômes et la régularisation des troubles circadiens et du sommeil peut améliorer les résultats du traitement dans la dépression.



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Cognitive symptoms of depression as major targets for antidepressants

by G. M. Goodwin, United Kingdom

Cognition is the word often used to describe the fundamental human capacity to think. Its disturbance in depression is probably what most bothers patients and their families, and not the symptoms that are usually used to measure and diagnose the condition. There is an increasing interest in applying to depressive illness the experimental methods developed in neuroscience for understanding cognitive function. These initially focused on memory, attention and executive function, all of which are domains influenced by depression and its severity. It has also become clear that depression has an enduring impact on memory function, with major implications for neurobiological explanations of depression and its sequelae. Direct investigation of how emotion is represented in the brain is also of great emergent interest and relevance. Cognitive function has thus become an increasingly central target for the investigation of drug action and the development of compounds that selectively target the most important cognitions affected in depression. These developments have also reignited interest in patient experience and the possibility that emotions may be blunted in depression, but also as a consequence of its treatment.

Medicographia. 2008;30:35-39. *(see French abstract on page 39)*

Keywords: *antidepressant; cognitive symptom; depression*

Words limit how we think. Some words, like depression, are tired and pale expressions of what they purport to describe. Depression is "a wimp of a word," according to William Styron, describing his own experience in *Darkness Visible: A Memoir of Madness*. We may also be too familiar with the idea that depression is a constellation of symptoms rather than a profound disturbance of cognition. The word cognition (or cognitive) refers to the action or faculty of knowing, a fundamental human activity. At its simplest it equates to thinking. Its disturbance in depression is what most bothers patients and their families, even if the concepts used to capture it are unfamiliar. Thus, in neuroscience applied to mood disorder, it has acquired a more particular meaning. To use the term "cognitive" is, therefore, rather too broad in the present context, but it is given credibility by use. It might also be more sensible to talk about neuropsychological function since that has the implication of a more laboratory-based investigation of how the brain, or traditionally the mind, actually works. The key finding is that neuropsychological function, estimated experimentally, is manifestly abnormal when patients become mood disordered, be they depressed or manic.

Performance in tests of particular domains of activity has long been a subject of scientific enquiry. Such functions are essentially the emergent properties of the brain itself. How they go wrong in key illnesses may be important for how we understand the illness itself and its basis in brain. Moreover, they may provide biomarkers for how new drugs can be developed. This is increasingly the current interest in the field and why it is developing as it is.

The investigation of cognition divides into two broad approaches, depending upon how explicitly we include emotional valence as a key experimental variable. The best known approach to attention, memory, and executive function has traditionally tested such functions independently of emotion. Thus one may ask whether mood disorder is associated with abnormal orientation or allocation of attention to stimuli and whether attention can be normally sustained. In relation to memory and executive function, it is possible to investigate how well depressed or manic patients perform relevant tasks and, moreover, whether having been depressed impairs performance independent of current mood.

SELECTED ABBREVIATIONS AND ACRONYMS

LEIS	Laukes Emotional Intensity Scale
SSRI	selective serotonin reuptake inhibitor

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Does depression leave a scar? The more recent approach introduces emotion into these domains. We can increasingly study emotional processing directly using behavior and imaging. We are also returning to actual patient experience, which is not always well served by symptom scales.

The elements of cognitive function that co-vary with mood

The starting point for this field has been the identification of elements of cognitive function that covary with mood. The core features of acute depression include the way in which thoughts and actions are slowed, memory is subjectively disturbed, and work and concentration are impaired. It is these features of the acutely depressed state, rather than simply sadness itself, that define the illness that we describe as a major depressive episode.

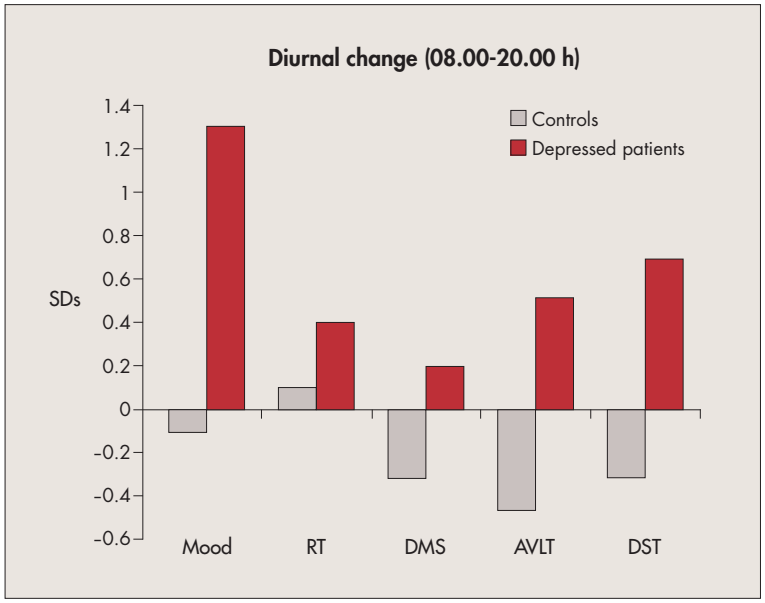

Figure 1. Changes in mood and reaction time (RT). Delayed match to sample (DMS), list learning (AVLT) and digit symbol substitution between 08.00 and 20.00 hours in depressed patients compared with controls. Change expressed as standard deviation units (SDs) on the vertical axis.

Modified from reference 1: Moffoot AP, O'Carroll RE, Bennie J, et al. Diurnal variation of mood and neuropsychological function in major depression with melancholia. *J Affect Disord.* 1994;32: 257-269. Copyright © 1994, Elsevier B. V.

It turns out that these symptoms can easily be measured. Slowing of thoughts and actions can be captured as reaction times to appropriate stimuli; memory, while subjectively disturbed, can also be objectively investigated by looking at how well we learn and remember lists; and impairment of work and concentration can be modeled by looking at tests of how we organize our attentional capacity to execute executive tasks in a laboratory setting. So-called tests of executive function are all impaired in patients with mood disorder, and they reflect, in all probability, valid experimental correlates of symptoms that are important in the disease.

The way in which these symptoms vary in time with mood itself is perhaps best illustrated by studying the spontaneous variation in mood that takes place in many patients from morning to evening. When my group studied this about 15 years ago, we could show very convincingly that the mood swing in the patients with depression was related to changes in neuropsychological function.[1] Thus, at baseline, patients studied in the early morning showed clear lengthening of reaction time, impaired function on list learning (the auditory/verbal learning test) and the delayed matched sample test from the Cambridge Neuropsychological Test Automated Battery, and poor performance on the digit symbol substitution test which taps executive function *(Figure 1)*. When examined and compared 12 hours later, depressed patients showed a significant mood upswing, accompanied by improved performance on all measures. Performance in nondepressed controls, on the other hand, actually declined as the day went on, presumably from fatigue. The study design controlled for the effects of concomitant medications in severely ill patients.

At that time, we also compared patients with different severities of depression, specifically those showing endogenous features with those showing neurotic features, and controls. In this study[2] we were able to compare performance in memory, attention and executive tasks. Both clinical groups showed impairments of episodic memory, which did not differ dramatically with the presence or absence of endogenous features. Executive function was significantly more impaired in patients with endogenous symptoms, while functional impairment was of course greater. But we were unable to demonstrate convincingly that this represented a simple difference of types. It could have been a relation between cognitive function and symptom severity.

This issue has been addressed using reaction time measures by Gordon Parker's group at the University of New South Wales.[3] When plotted independently, results in a large group of patients that followed a unimodal distribution when compared using symptoms showed a bimodal distribution when compared using retardation as a measure. This bimodality loosely corresponds to the endogenous/neurotic distinction. In other words, we have clear evidence that episodic memory and executive function are always more impaired in endogenous depression and that the impairment is related to symptom severity. Moreover, retardation, which predicts impairment on speed tests, is indeed a potential defining characteristic of the more severe syndrome we refer to as endogenous depression.

Although cognitive impairments showed diurnal variation over 24 hours, the patients continued to be depressed. The question then is whether cognitive function recovers with complete symptom remission. The basic answer is "Yes, but incompletely." While some studies, particularly in older patients, have suggested enduring residual deficits in memory and executive function,[4-6] no such deficits are present in younger patients, or at least they have not been detected in small samples. This recovery of function has a potential utility for clinical trials that has never been realized, either as a marker of severity or as an index of change. Since, arguably, neuropsychological measures are more objective and less susceptible to bias than traditional rating scales, this is both surprising and regrettable. Sever-

ity is an important criterion for entry into drug studies, which could be indexed by impaired mnemonic function. Moreover, cognitive function might serve as a potentially more specific target for particular drug effects. For example, it might be the case that some drugs have a more convincing effect on cognitive symptoms than others. We simply have no knowledge in this area as far as most psychotropic drugs are concerned. However, our group has shown in healthy volunteers that the selective serotonin reuptake inhibitor (SSRI) citalopram has the potential to improve memory function. In a way this is quite a surprising result because it is uncommon to see drugs improving function in healthy young people.[7]

Complete recovery of memory function depends on the duration of lifetime depression (P. Gorwood et al, submitted). Because the impairment is slight, it is only detectable in a very large patient sample. The major group of patients in whom cognitive function more detectably fails to recover fully on symptom remission is bipolar disorder. Bipolar I patients have been studied many times while euthymic and the consistent finding is impaired list learning. The cause remains unelucidated. It may well be related to residual depressive symptoms, which are actually subsyndromal, but nevertheless have an impact on memory. It could also be a drug effect. Perhaps most interestingly, it could be the consequence of repeated episodes of illness.[4,8-10] This also appears to be the case for sustained attention, where patients show substantial decrements of function.[4,5] It does not appear to be a simple working memory effect, but more likely related to a true deficit in the accuracy of signal detection. In general, bipolar patients may show bigger deficits because they usually have more intense illness courses than unipolar cases.

The neural substrate of enduring cognitive impairment

If depression is associated with impaired memory, what is the likely mechanism? The structural correlates of impaired brain function in depression are interesting. The original finding[11] in chronically refractory depression was that hippocampal volume was bilaterally reduced with correlated impairments of memory function. The hippocampus is an area of the brain in which synaptic changes and neurogenesis are most readily demonstrated. It may be more sensitive to apparently functional changes of many kinds than other areas. Other studies in clinic samples suggest that hippocampal size correlates with duration of depression,[12] as if depression itself were a toxic exposure for the brain. It is possible, but unproven, that this is mediated by hypercortisolemia, which has proved toxic in animal experiments.[6,13]

Other circumstantial findings strengthen the link between depression and impaired neurogenesis. Antidepressants and electroconvulsive therapy increase neurogenesis in animal models, supporting the hypothesis that antidepressants work at least in part by restoring neurogenesis and synaptic density in depression-critical brain areas.[14] This idea would probably not have made sense had we not been able to detect functional impairments related to these areas of interest. Further, polymorphism in the gene encoding brain-derived neurotrophic factor[15] appears to modulate memory function in healthy volunteers,[16] and can be expected to do so in patients with depression.

A final point, following this presentation of the key findings specifically related to memory function and the hippocampus, is that the same neuronal mechanisms may operate less detectably in other neuronal systems. The far-reaching impact of mood on cognitive function and the emotional life of the depressed individual is likely to reflect this.

The neurobiology of emotional processing

As the preceding paragraphs illustrate, neuropsychological investigation proceeded from tests of nonemotional processing, eg, the ability to remember a list of neutral words. The relevance of the findings followed from the way in which such tests assayed function in brain areas, such as the hippocampus, that appear particularly vulnerable to the effects of mood change. In recent years, experimental approaches to the direct neural representations of emotional experience have become possible, at the stages of perception, recollection, experience, and expression. Many different methods have been used to characterize the changes in these dimensions caused by mood disorder. It will only be possible to give a few examples.

The most obvious approach to mood is to induce it directly. There are traditional problems with the authenticity of such experimentation (do subjects tell the truth when they know what the experimenter expects of them?), but brain imaging goes some way to validate it. Mood induction procedures have shown changes in frontal and limbic areas that have been implicated for other reasons in mood disorder. With induced sadness and in depression, positron emission tomography identifies increased blood flow in the anterior insula and subgenual region of the ventral anterior cingulate gyrus accompanied by decreases in the neocortical (right dorsolateral prefrontal and inferior parietal) regions. With recovery from depression, the reverse pattern, involving the same regions, is observed. Thus, reciprocal changes involving subgenual cingulate and right prefrontal cortex occur with both transient and chronic changes in negative mood.[17] The region of the subgenual orbital frontal cortex (Brodmann's area 25) is overactive in resistant depression.[18] This lack of reactivity gave rise to the hypothesis that stimulation of white matter adjacent to the area would be an effective treatment for depression. The technique of deep brain stimulation focused in or adjacent to the area which is least reactive in patients is already widely and successfully used to treat movement disorders. Preliminary results have been encouraging in highly refractory depressed patients. This is one of the first examples of modern clinical neuroscience research leading to a translational advance in treatment.

The recognition of emotions expressed by others is, in some ways, a less contentious way in which to get at emotional representation within the brain. The basic emotions of sadness, happiness, anger, surprise, disgust, and fear are expressed on the faces of others. How we recognize them must tell us something about the way in which we represent these emotions. The parsimony of brain representation suggests that this may also be relevant to how we experience them. Our group has examined the effects of medication on a variety of tests addressing the quality of emotional expression. The recognition of fearful or happy faces, for example, can be examined by morphing exemplars of fear or happiness between a clear and unequivocal expression to an expression of neutrality using digital methods. When one then looks at the detectability of the expression across the range, one sees increased accuracy as one would expect when moving from a neutral to a fully fearful face. Treatment with citalopram or reboxetine reduces this facilitation. Subjects become less sensitive to fearful expressions on the faces of others.[19]

There is no corresponding impact on the ability to detect happiness in the faces of others. The implication may be that one way in which antidepressants work, or at least one property that some antidepressants may have, is to reduce the processing of fear in central structures. In the case of citalopram, we have confirmed that this is likely to be at the level of the amygdala, since changes in that brain area occur over the same time scale as the behavioral change just described.[20] Indeed, effects are discernible in other experiments within as little as 20 minutes after infusion of citalopram.[21] It therefore represents an action that is extremely quick and potentially relevant to how patients subsequently perceive the world.

Any effect that was confined simply to fear would potentially reflect only the actions of an anxiolytic, such as lorazepam.[22] There are further effects associated with antidepressants which suggest that they regulate how we access positive and negative memory items. This is clearly closer to the ideal properties that might be required of an antidepressant. We can ask subjects or patients to categorize words on the basis of whether or not they regard them as insulting or generous: would they like to be described personally by adjectives such as obnoxious, original, ugly, etc? One can then measure, firstly, the speed at which patients respond, and, secondly, the ease with which they spontaneously recall different words after a 30-minute delay. Citalopram and reboxetine both speed the acute response to positive words and facilitate the recall of positive words after a fixed delay. In simple terms, the positive words are better encoded and more easily retrieved under the actions of citalopram or reboxetine than placebo.

Our hypothesis is that such effects may not just be incidental properties of antidepressants, but have the potential to explain their antidepressant effects. It is notable that these effects are extremely acute and yet the overall speed of response to antidepressants such as citalopram and reboxetine is relatively slow, taking 4 to 6 weeks to be clinically significant. Change begins immediately, however.[23] A possible explanation is that the actions of antidepressants are indeed acute and immediate, but the necessary adaptive changes, the relearning of different contingencies with different emotional biases both in perception and memory, are the basis for the actual antidepressant response. On this basis, antidepressants should be developed and screened for their acute capacity to modify emotional representations. This would clearly have implications for how we develop new compounds. The alternative view is that such effects are of interest, but they may really constitute side effects of the drugs. There is a current vogue to favor a more downstream effect, eg, on growth factors with a more direct impact on hippocampal and amygdalar plasticity.[24] If this indeed forms the basis of antidepressant action, then clearly one should be trying to speed that process up, independently of whether or not there are immediate effects on the perception of affect and its recollection.

Subjective emotional experience in patients taking psychotropic drugs

Just as measures of cognition may tell us how to detect the wanted effects of treatment, they may also guide us in avoiding its unwanted effects. The investigation of emotional experience under antidepressants suggested a further interesting interpretation of the findings. Patients appear to perceive fearful facial expressions less readily while taking an SSRI (citalopram). While this could correct a system over reactive to fear stimuli, it might overcompensate some individuals and make them less emotionally connected with their surroundings. Could this sometimes be an unwanted effect of SSRI treatment? This possibility is supported by the most subjective and unscientific evidence: clinical anecdote. Some patients who have taken SSRIs are clearly aware of "emotional blunting" on these drugs. The most voluminous evidence comes from the spontaneous patient reports widely available on the internet. Such informal networks of experience are potentially very useful when harnessed to more controlled studies. This is now required for emotional experience.

A potentially related side effect is impaired sexual responsiveness, a relatively common and well documented side effect of SSRIs. A small group of patients with SSRI-induced sexual dysfunction were investigated using the Laukes Emotional Intensity Scale (LEIS). This includes items such as reduced ability to cry, reduced ability to care about others, lack of creativity, and inability to express feelings. While this is confounded in such a study by depression itself, total LEIS scores did not correlate with total scores on the Hamilton Depression Rating Scale in this study. This patient subgroup appeared to have impaired emotional reactivity in a variety of areas, not just sexual response.[25] The absence of sexual side effects may nevertheless be an important marker of a more benign effect on emotional response generally.

The challenge is now to devise a systematic way of measuring the experience of emotional blunting that captures qualitative patient experience and can be validated quantitatively in larger groups of representative patient samples. It should also be possible to compare different treatments head to head. We are currently involved in the necessary qualitative work to tailor a scale to patient experience. The first formal comparison will be between escitalopram and agomelatine, since the latter should have an advantage from the point of view of such side effects.[26] In conclusion, neuroscience has been used to further understanding of cognitive and executive function, memory, and attention. These are all domains that are influenced by depression and its severity. Depression has an enduring impact on memory function that has important implications for neurobiological explanations of depression and its sequelae. Direct investigation of how emotion is represented in the brain is of great emergent relevance. Cognitive function has become a central target for investigating drug action and developing new compounds that selectively target the most important cognitions affected in depression. ❐

REFERENCES

1. Moffoot AP, O'Carroll RE, Bennie J, et al. Diurnal variation of mood and neuropsychological function in major depression with melancholia. *J Affect Disord*. 1994;32:257-269.
2. Austin MP, Ross M, Murray C, O'Carroll RE, Ebmeier KP, Goodwin GM. Cognitive function in major depression. *J Affect Disord*. 1992;25:21-29.
3. Parker G, Hadzipavlovic D, Wilhelm K, et al. Defining melancholia–properties of a refined sign-based measure. *Br J Psychiatry*. 1994;164:316-326.
4. Clark L, Iversen SD, Goodwin GM. Sustained attention deficit in bipolar disorder. *Br J Psychiatry*. 2002;180:313-319.
5. Clark L, Kempton MJ, Scarna A, Grasby PM, Goodwin GM. Sustained attention-deficit confirmed in euthymic bipolar disorder but not in first-degree relatives of bipolar patients or euthymic unipolar depression. *Biol Psychiatry*. 2005;57:183-187.
6. O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *Am J Psychiatry*. 2004;161:2081-2090.
7. Harmer CJ, Bhagwagar Z, Cowen PJ, Goodwin GM. Acute administration of citalopram facilitates memory consolidation in healthy volunteers. *Psychopharmacology*. 2002;163:106-110.
8. Ferrier IN, Stanton BR, Kelly TP, Scott J. Neuropsychological function in euthymic patients with bipolar disorder. *Br J Psychiatry*. 1999;175:246-251.
9. Martinez-Aran A, Vieta E, Colom F, et al. Cognitive dysfunctions in bipolar disorder: evidence of neuropsychological disturbances. *Psychother Psychosom*. 2000;69:2-18.
10. Robinson LJ, Thompson JM, Gallagher P, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord*. 2006;93:105-115.
11. Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment-resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br J Psychiatry*. 1998;172:527-532.
12. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci*. 1999;19:5034-5043.
13. McEwen BS. Effects of adverse experiences for brain structure and function. *Biol Psychiatry*. 2000;48:721-731.
14. Santarelli L, Saxe M, Gross C, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*. 2003;301:805-809.
15. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. *Biol Psychiatry*. 2006;59:1116-1127.
16. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*. 2003;112:257-269.
17. Mayberg HS, Liotti M, Brannan SK, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry*. 1999;156:675-682.
18. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005;45:651-660.
19. Harmer CJ, Hill SA, Taylor MJ, Cowen PJ, Goodwin GM. Toward a neuropsychological theory of antidepressant drug action: increase in positive emotional bias after potentiation of norepinephrine activity. *Am J Psychiatry*. 2003;160:990-992.
20. Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biol Psychiatry*. 2006;59:816-820.
21. Del-Ben CM, Deakin JF, McKie S, et al. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an fMRI study. *Neuropsychopharmacology*. 2005;30:1724-1734.
22. Paulus MP, Feinstein JS, Castillo G, Simmons AN, Stein MB. Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. *Arch Gen Psychiatry*. 2005;62:282-288.
23. Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry*. 2006;63:1217-1223.
24. Manji HK, Quiroz JA, Sporn J, et al. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol Psychiatry*. 2003;53:707-742.
25. Opbroek A, Delgado PL, Laukes C, et al. Emotional blunting associated with SSRI-induced sexual dysfunction. Do SSRIs inhibit emotional responses? *Int J Neuropsychopharmacol*. 2002;5:147-151.
26. Hamon M, Bourgoin S. Pharmacological profile of antidepressants: a likely basis for their efficacy and side effects? *Eur Neuropsychopharmacol*. 2006;16:S625-S632.

LES SYMPTÔMES COGNITIFS DE LA DÉPRESSION: CIBLES PRIORITAIRES POUR LES ANTIDÉPRESSEURS

« Cognition » est un mot souvent utilisé pour désigner l'aptitude humaine fondamentale à penser. Les troubles cognitifs sont probablement ceux qui gênent le plus les patients déprimés et leur famille et non les symptômes habituellement utilisés pour mesurer et diagnostiquer la maladie. L'application à la maladie dépressive des méthodes expérimentales développées en neurosciences pour comprendre la fonction cognitive rencontre un intérêt croissant. À l'origine, ces méthodes étaient destinées à étudier la mémoire, l'attention et la fonction exécutive, tous domaines influencés par la dépression et sa sévérité. Il est également devenu clair que la dépression a un impact durable sur la mémoire, ce qui a de nombreuses implications pour la compréhension neurobiologique de la dépression et de ses séquelles. L'exploration directe de la représentation de l'émotion dans le cerveau a également démontré son intérêt et sa pertinence. La fonction cognitive a ainsi acquis une place de plus en plus centrale dans la recherche sur le mode d'action des médicaments et le développement de produits ciblant sélectivement les fonctions cognitives les plus importantes affectées par la dépression. Ces développements ont aussi renouvelé l'intérêt pour l'expérience des patients et la possibilité que l'émoussement des émotions soit non seulement dû à la dépression, mais aussi à son traitement.

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How should the core symptoms of depression be assessed?

by B. Falissard, France

How the core symptoms of depression should be assessed depends on how they are defined. Physiological and/or psychopathological considerations may be essential to the definition, but statistical considerations are also important, notably with respect to the crucial notion of unidimensionality. By definition, a set of items is unidimensional if there is a variable that alone "explains" all the inter-item correlations. With quantitative measures, factor analysis is potentially a good statistical technique for assessing unidimensionality. Goodness-of-fit tests, however, are less appropriate. Scree plots of the eigenvalues for the correlation matrix of the items are an interesting alternative to factor analysis, especially when using simulated data, as in parallel analysis. Other methodological considerations in assessing the core symptoms of depression include the question of categorical versus dimensional measurement. Each has its advantages: clinical relevance for categories, sensitivity to change, and conceptual relevance for dimensions. Also important is the question of who is the most appropriate assessor of the core symptoms of depression: the patient, or the physician after clinical interview? In psychiatry, unlike in most other areas of subjective measurement, the clinician has always been considered more reliable—a tradition currently under challenge.

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Keywords: *clinician assessment; core symptom; depression; self-assessment; unidimensionality*

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Most papers in this issue focus on clinical questions concerning core symptoms in depression. This paper concentrates on methodology, beginning with the hoary problem: should the definition of core symptoms be categorical or dimensional? It then discusses a clear trend in psychiatric measurement away from the clinical and towards the field of psychoexperimental research. Thirdly, it addresses the much debated issue of who is the most appropriate assessor of these core symptoms: clinician or patient? The concluding and most important question discussed is whether, and under what conditions, a formal psychometric definition of the core symptoms of depression is possible.

Category versus dimension

Is psychiatric disease, such as depression, categorical or dimensional in nature? This question inevitably relates to another: what is the definition of a psychiatric disease? The answer is not so simple, as shown by a recent symposium on the subject at the American Psychiatric Association's annual meeting. Psychiatric disease can be viewed in various lights, including as a historical semiological construct, a specific physiological or psychological weakness in human beings, a legal tool, or a simple word used in the media.

Although the issue may be theoretically complex, routine clinical experience favors a dimensional view of psychiatric phenotypes, especially depression. Thus a patient may be "more or less" depressed. So why use a categorical construct such as major depressive disorder? One answer is that therapeutics is basically categorical. Prescribing an antidepressant, electroconvulsive therapy, or psychotherapy, or recommending hospitalization, is usually a binary decision, and thus categorical by essence. Since clinicians are nothing if not therapists, it is likely that they have forced diagnoses to be categorical to help them optimize their treatment choices.

However, the optimal way to deal with patients is not necessarily the optimal way to deal with research. Clinical trials in depression, for instance, require outcome measures that are sensitive to change. Categorical measures are generally less efficient in this regard than dimensional measures. Hence even if categorical outcomes, such as treatment response or remission, are often valued because they are close to clinical practice and because differences are easier to interpret, dimensional outcomes have the advantage of being statistically more efficient and perhaps closer to a natural representation of what we call "depression."

Clinical versus psychoexperimental assessment

As clinical trials with antidepressants increasingly fail to differentiate placebo from active comparators, there is a temptation to identify outcome measures that are highly sensitive to change. A solution sometimes proposed is to abandon clinical measures for the currently more fashionable field of psychoex-

perimental measures, which may, one day, acquire valuable advantages, such as improved measurement properties or objectively robust validity. At the moment, however, they suffer from a lack of clinical relevance: with the type of outcome they offer, it is impossible to tell whether or to what extent patients are improved in their daily lives. This is totally unacceptable in clinical trials that are designed to obtain drug approval and even more so for insurers needing to price a medication.

Core symptom rating by clinician or patient?

Depression is a subjective concept, defining subjective as "belonging to the thinking subject rather than to the object of thought."[1] Subjective entities include pain, quality of life, fatigue, satisfaction, depression, and anxiety. Psychiatric measures are an exception among subjective measures: clinician rating scales are implicitly considered as the gold standard, whereas in other areas things are quite the reverse. There are many reasons for this, none of which are wholly evidence-based:

- Psychiatric measures are older than other subjective measures that were developed in a specific political context. In the 1970s, there was a move for patients to liberate themselves from the "yoke" of physicians. This required outcome measures sourced more directly from the patient than from the clinician, as illustrated by the emergence of patient-reported outcome. The frequent preference in subjective measurement for patient-reported outcome over clinician-reported outcome is not based on solid scientific argument.
- Self-report depression questionnaires may be biased in that depression may alter the patient's ability to assess himself sensibly, in particular at the start of a depressive episode, when symptoms are most severe.
- Regulatory agencies, such as the Food and Drug Administration or European Medicines Agency, favor clinician rating scales.
- Most double-blind randomized controlled studies lead to smaller effect sizes with self-report questionnaires than with clinician rating scales. Clinician scales tend to be more sensitive to change and thus more efficient in both economical and ethical terms.

However, all these reasons are debatable[2]:

- The view that patient-reported outcome is nonscientific is an opinion, or at most a hypothesis.
- There is, to our knowledge, no scientific evidence that psychiatric patients' assessment of themselves is any more biased than that of other patients, eg, cancer patients. Even in schizophrenia, many self-rated questionnaires have shown good reliability.[3]
- Regulatory agencies may revise their position on self-rated questionnaires in depression.[4]
- The effect-sizes argument against self-report questionnaires stumbles against the finding that effect sizes have not differed in some studies using twin instruments in a patient-reported version and a clinician-reported version.[2] Also, any differences could be methodological in origin[5]: clinicians in placebo-controlled randomized trials may detect subtle cues that help them identify the patients on active medication, and they may then unconsciously overestimate the improvement of patients under active treatment.

Some arguments favor patient-reported depression questionnaires. One is their lower cost, another is their greater ecological validity. Thus by using interactive voice response systems, patients can experience these questionnaires in their everyday context rather than in a medical setting.

In summary, there is no conclusive evidence for the superiority of either clinician or patient assessment in depression. In practice, this is a strong argument for developing both types of instrument and using them in clinical trials.

Identifying core symptoms in depression: the statistical viewpoint

This paper proposes a purely statistical definition of core symptoms: they should correspond to the subset of traditional symptoms of depression that constitute a unidimensional family. The question now is: why and how? Unidimensionality is a central concept in psychometrics. Firstly, psychometricians postulate that a measure should only concern a single attribute. The most classic illustration of this point of view was by McNemar[6]:

> *Measurement implies that one characteristic at a time is being quantified. The scores on an attitude scale are most meaningful when it is known that only one continuum is involved. Only then can it be claimed that two individuals with the same score or rank can be quantitatively and, within limits, qualitatively similar in their attitude towards a given issue. As an example suppose a test of liberalism consists of two general sorts of items, one concerned with economic and the other with religious issues. Two individuals could thus arrive at the same numerical score by quite different routes. Now it may be true that economic and religious liberalism are correlated, but unless highly correlated, the meaning of scores on a such a composite is questionable.*

More formally, in some measurement models developed for instruments comprising several items (item response models, in particular), unidimensionality of the items composing the instrument is a prerequisite. We shall begin by defining the property of unidimensionality in a set of items. For this we will turn to factor analysis, and we shall discover that, in this context, principal component analysis is an essential tool.

◆ *Definition*

For a number of years the very definition of unidimensionality varied noticeably from one author to another. Since the McDonald's 1981 paper,[7] a consensus has gradually emerged: a set of items is unidimensional if there is a variable, which, on its own, "explains" all the correlations observed be-

tween items. In formal terms, if this variable is maintained at a constant level in a sample of subjects, then items in this sample are independent of each other. This reflects the existence of a "single core" common to all the items: once this core is established, the items behave independently of each other.

It was Spearman who originated this definition in 1904, setting it out in as yet sketchy form in a celebrated article[8] that examined the unidimensionality of a set of cognitive items relating to the concept of intelligence:

> *All branches of intellectual activity have in common one fundamental function (ie, intelligence), whereas the remaining or specific elements of the activity seem in every case to be wholly different from that in all the others.*

Spearman developed a statistical technique to bear out a property of this sort: factor analysis, namely (in its one-factor version), a model in which the response to an item is the summation of a linear function of a characteristic common to all items and a term which groups together measurement error and a part specific to each item.

However, if a set of items fitting a one-factor analysis model is indeed unidimensional, the reverse is not true, in particular because the one-factor analysis model is linear in the common characteristic. However, in practice, this sort of situation is rare.[7] A one-factor analysis model is thus, as a first approximation, a necessary but insufficient condition of unidimensionality, at least when responses to items may be considered as numerical random variables.

Moving on from this conclusion, the question of the unidimensionality of a set of items looks quite simple. It is sufficient, in theory, to statistically test the fit of the data to a one-factor analysis model. Some software enables this sort of test, but the results are not easy to interpret. Indeed, whatever the characteristic to be measured, we can be sure that the items used in the instrument are never truly unidimensional. Furthermore, if a validation study is conducted on a large number of subjects, the goodness-of-fit test will be very powerful, and the chances of the unidimensionality hypothesis being rejected will inevitably be high. This ends us up in the paradoxical situation in which, by studying a large sample, we reduce the chance of demonstrating what we intend to demonstrate—in other words, we would be better off carrying out the study in a small sample, which would be absurd.

To get round this paradox that in fact bedevils all the model-fitting issues, we have fit indices and parsimony criteria, such as the root mean square error of approximation, normed fit index, Akaike information criterion, and Bozdogan index of information complexity.[9] They have the advantage of flexibility, but the drawback of frequently reaching different conclusions. They are also based on unclear heuristics, which makes the interpretation of results somewhat arbitrary. In practice, possibly in reaction to this methodological vacuum, a unidimensionality indicator of a completely different kind is often used. This method considers the percentage of variance represented by the first principal component. But why is principal component analysis associated with the concept of unidimensionality?

◆ *Principal component analysis*

Principal component analysis is a multivariate technique for reducing the number of dimensions in a set of variables, while preserving the "information" contained in these variables as much as possible. In statistics, "information" is classically assimilated to variance. Thus, if the first principal component represents, on its own, a large part of the variance of the variables, it is tempting to conclude that a single dimension suffices to resume the variables overall. It is then possible to consider that they form a unidimensional whole.

Of course, this is not in line with the definition of unidimensionality given above, for at least two reasons. Firstly, principal component analysis and factor analysis are two different methods. In practice, however, the numerical results yielded by these two techniques are generally very close[10]: the percentage of variance represented by the first principal component approximates to the share of variance represented by the common factor in a one-factor analysis model.

But this does not get us very far. The share of variance represented by the common factor does not enter into the definition of unidimensionality. Either the model fits, or it doesn't. The fact that the common factor has high variance is not relevant. Nevertheless, this sort of attitude is not very pragmatic: a unidimensional set of items in which the common factor represents only a very small percentage of the variance leads to an instrument that is practically useless. In a frequently quoted article, Cronbach[11] explained:

> *For a test to be interpretable […] what is required is that a large proportion of the test variance be attributable to the principal factor running though the test. […] The proportion of the test variance due to the first factor among the items is the essential determinant of the interpretability of the scores.*

In practice, therefore, two stages are required:
- The first determines whether or not the first principal component emerges in isolation from among the components as a whole (are the items, qualitatively, uni- or multi-dimensional?).
- The second assesses the weight of this first principal component in the overall variance of the instrument (is the first component strong or not?).

The statistical tool that can be used in each of these stages is the eigenvalue diagram or scree plot,[12] an essential instrument for determining unidimensionality in a set of items.[13] An extremely simple example illustrates how results can be interpreted from a set of geometrical representations. Let us consider a 3 item instrument administered to 27 subjects. As each subject undergoes three evaluations, the data can be represented geometrically by 27 dots in a three-dimensional space *(Figure 1)*.

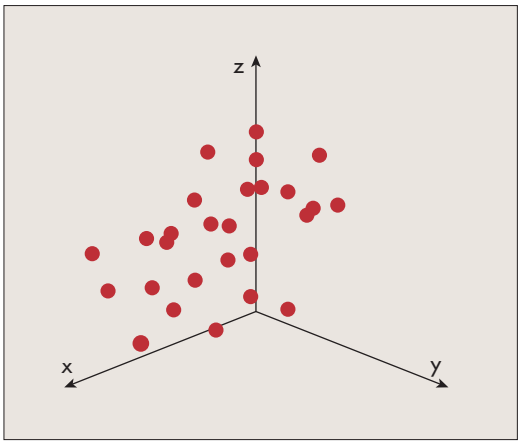

Figure 1. Geometrical representation of three items (x, y, and z) measured in 27 subjects.

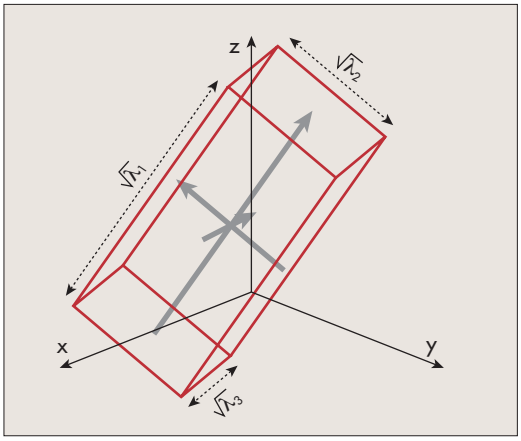

Figure 2. Principal components of preceding data.

Principal component analysis of the data looks for the three directions in which the scatter of dots spreads *(Figure 2)*. The scatter spreads more or less along the principal components. Numerically, the square root of the eigenvalue λ_1 associated with the first principal component indicates how closely the dots are dispersed along this component. The same is true for λ_2 and λ_3 in relation to the second and third principal components. If λ_1 is very much higher than λ_2 and λ_3, the dots will be situated more or less along a straight line: this means that they form a unidimensional whole. A scree plot is the simple graphic representation of eigenvalues λ_1, λ_2 and λ_3 *(Figure 3)*. The principle remains the same when applied to actual examples exceeding three items: 136 patients hospitalised for depression were assessed on admission using the Hamilton depression rating scale (unpublished data). Is this instrument unidimensional in this patient sample? The scree plot is given in *Figure 4*. How should this result be viewed? The hypothesis of unidimensionality can be rejected outright: there is no marked break after the first component. But how many dimensions can be distinguished? None? Possibly two? It is not easy to answer this question from this diagram alone.

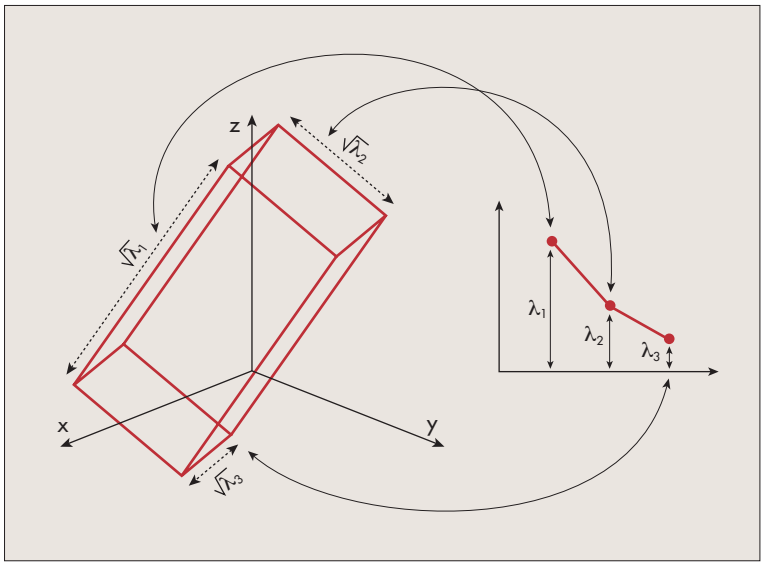

Figure 3. Construction of a scree plot.

Some simulations, such as parallel analysis,[14] offer partial answers to these questions. Implementation involves simulating measures for 17 items in 136 patients using random numbers, followed by principal component analysis of the simulated items, and finally comparison with the scree plot in *Figure 4*. This procedure produces the result shown in *Figure 5*. Compared with the plots obtained by simulation, the first two dimensions of the Hamilton scale appear to stand out from the rest. Thus, the instrument is not unidimensional in this population.

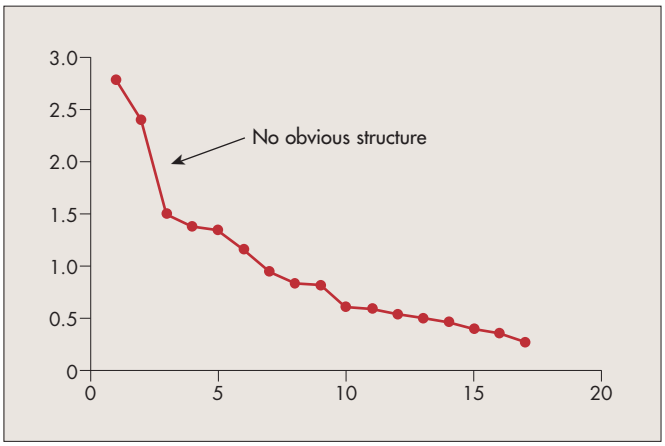

Figure 4. Scree plot for 17 items in Hamilton's depression rating scale.

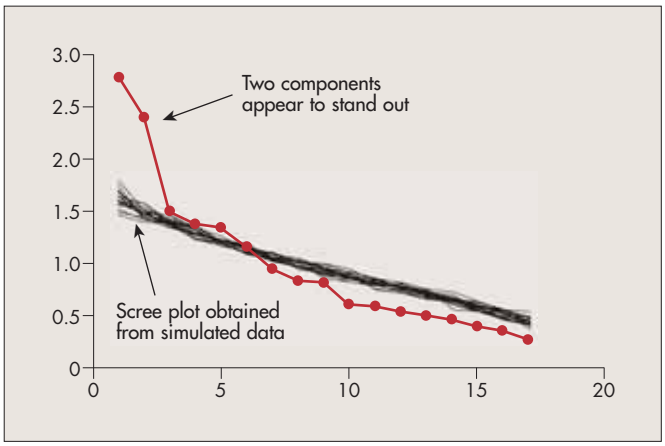

Figure 5. Use of numerical simulations to determine a dimensional structure.

Conclusion

Practical assessment of core symptoms in depression raises classic methodological considerations, such as the identity of the ideal assessor (patient or clinician, or both), and the omnipresent choice in psychiatric research between categorical and dimensional measures (and the possible calculation of a cutoff).

Each is potentially useful: categories are clinically relevant, while dimensions are sensitive to change and conceptually relevant. More profoundly, how core symptoms should be assessed depends on how they are defined. In this regard, statistical considerations are as important as physiology and psychopathology, with the notion of unidimensionality being particularly crucial. With quantitative measures, factor analysis successfully operationalizes the definition of unidimensionality. However, goodness-of-fit tests are of a questionable value. Scree plots of the eigenvalues of the correlation matrix of the items offer an interesting alternative to factor analysis, especially when using simulated data, as in parallel analysis. ❐

REFERENCES

1. Modern Language Association (MLA). Dictionary.com Unabridged (v 1.1). Retrieved May 14, 2007 from http://dictionary.reference.com/browse/subjective.

2. Rush AJ, Trivedi MH, Carmody TJ, et al. Self-reported depressive symptom measures: sensitivity to detecting change in a randomized, controlled trial of chronically depressed, nonpsychotic outpatients. *Neuropsychopharmacology.* 2005;30:405-416.

3. Falissard B, Bazin N, Hardy-Bayle MC. Outcome revealed by preference in schizophrenia (OPS): development of a new class of outcome measurements. *Int J Methods Psychiatr Res.* 2006;15: 139-145.

4. Food and Drug Administration (FDA). *Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.* Rockville, Md: US Department of Health and Human Services Food and Drug Administration; 2006.

5. Greenberg RP, Bornstein RF, Greenberg MD, Fisher S. A meta-analysis of antidepressant outcome under "blinder" conditions. *J Consult Clin Psychol.* 1992;60:664-669; discussion 670-677.

6. McNemar Q. Opinion-attitude methodology. *Psychol Bull.* 1946;43:289-374.

7. McDonald RP. The dimensionality of tests and items. *Br J Math Stat Psychol.* 1981;34:100-117.

8. Spearman CE. "General intelligence," objectively determined and measured. *Am J Psychol.* 1904;15:201-292.

9. Loehlin JC. *Latent Variable Models. An Introduction to Factor, Path, and Structural Equation Analysis,* 4th ed. London, UK: LEA; 2004.

10. Krzanowski WJ. *Principles of Multivariate Analysis, a User's Perspective.* Oxford, UK: Oxford University Press; 1990.

11. Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrika.* 1951;6:297-334.

12. Cattell RB. The scree test for the number of factors. *Multivariate Behav Res.* 1966;1:245-276.

13. Velicer WF, Eaton CA, Fava JL. Construct explication through factor or component analysis: a review and evaluation of alternative procedures for determining the number of factors or components. In Goffin RD, Helmes E, eds. *Problems and Solutions in Human Assessment: Honoring Douglas N. Jackson at Seventy.* Boston, Mass: Kluwer; 2000, 41-71.

14. Horn JL. A rationale and test for the number of factors in factor analysis. *Psychometrika.* 1965;30:179-185.

COMMENT ÉVALUER LES SYMPTÔMES MAJEURS DE LA DÉPRESSION ?

L'évaluation des symptômes majeurs de la dépression dépend de leur définition. Cette dernière peut reposer sur des critères physiologiques et/ou psychopathologiques, mais les critères statistiques, en particulier la notion essentielle d'unidimensionnalité, sont également importants. Par définition, un ensemble d'items est unidimensionnel si une seule variable « explique » toutes les corrélations inter-items. L'analyse factorielle, avec des items quantitatifs, est potentiellement une bonne technique statistique pour évaluer l'unidimensionnalité. Les tests d'adéquation sont toutefois moins appropriés. L'analyse factorielle peut être remplacée de façon intéressante par un diagramme des valeurs propres de la matrice de corrélation des items, particulièrement lorsque l'on utilise des données simulées comme dans l'analyse parallèle. L'évaluation des symptômes majeurs de la dépression peut faire l'objet de diverses approches, par exemple l'approche dimensionnelle face à l'approche catégorielle. Chacune a ses avantages : pertinence clinique pour les catégories, sensibilité au changement et pertinence conceptuelle pour les dimensions. La question de savoir qui du patient ou du médecin après l'interrogatoire clinique évalue le mieux les symptômes majeurs de la dépression est également importante. Contrairement à la plupart des autres domaines de mesure subjective, en psychiatrie, le médecin a toujours été considéré plus fiable, une tradition qui est actuellement contestée.

What symptom should be the primary treatment target in depression?

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The treatment of depression remains a mysterious combination of science and art. It is a science insofar as we know plenty about the neurobiology of depression in terms of genetic predisposition, neuroimaging changes, and the biochemical and neuroprotective effects of antidepressants. But it is an art in that we don't really know which therapeutic strategy will work for which individual. Patients' prioritization of their depressive symptoms varies with age, gender, occupation, and other sociodemographic variables. The elderly may emphasize the "meaningless of life," while younger adults identify fatigue or loss of energy as their primary concern. Culture is also important. In Asian societies, somatic symptoms such as headache and poor appetite are perceived as particularly distressing. They occupy much the same position as anhedonia or depressed mood for Western patients. An interesting study in white and Chinese elderly showed that Chinese elderly had a more positive attitude toward weight gain than their white counterparts. In Chinese society, weight gain in the elderly is perceived as "fa-foo" (literally, gaining happiness, ie, a marker of wealth and a happy family). Such people may be fat, but they are "happy fat." Generally speaking, anxiety and sleep disturbance are the most distressing symptoms of depression across all groups and they need to be prioritized in the treatment strategy. However, wise clinicians will always ask their patients which symptom matters to them most. Patients usually list several. The doctor can then work with the patient to identify which comes first. The order of symptom improvement is not only a relevant clinical factor, but also a window onto neural recovery by a depressed brain. No currently available antidepressant offers rapid relief for patients' two main complaints, namely anxiety and sleep disturbance. However, the combination of anxiolytics and hypnotics is invaluable for this purpose. Depressed mood will lift at a later stage, followed by the recovery of interest and pleasure. Damaged brain needs time to recover. The more complex the psychological function, the longer it takes to improve. Even recovered depressives remain psychologically different from healthy controls, in terms of negativity and hesitation. We still don't know whether this represents the residue of a depressive episode or a preexisting personality trait that predisposes to depression. Placebo can achieve improvements rates of up to 35% in depression. Since antidepressant efficacy averages no more than 50%, the margin of pharmacology over placebo is only 15%. Although placebo may be able to relieve all symptoms of depression, there is no evidence that it works better on some symptoms rather than others. True remission rates are much lower on placebo, by a difference well in excess of 15%. In other words, placebo may improve symptoms, but it tends not to eradicate them. Placebo appears particularly effective for somatoform symptoms that are often hard to classify as psychological, cognitive, or physical. But it has no place in long-term strategy, probably because depression is a systemic disease encompassing a constellation of symptoms that can only be cured once the depressive disease is itself cured. Applying the results of scientific research to clinical practice is a constant challenge. A well-designed clinical trial may generate statistically significant data packaged in a beautifully written paper. But the research setting is often too abstracted from clinical reality. It is thus no surprise that some costly studies should have failed to impact clinical behavior. ❐

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Major depressive episode is defined as a period of at least 2 weeks of depressed mood with suicidal ideation and abnormalities of neurovegetative function (altered appetite, weight loss, sleep disturbance [early awakening]), psychomotor activity (loss of energy and interest, agitation, retardation), and cognition (feelings of worthlessness, hopelessness, and inappropriate guilt). A frequent additional feature is diurnal variation (morning depression). While emotional symptoms such as depressed mood and loss of interest have traditionally been viewed as the core symptoms, the prevalence and importance of anxiety and physical symptoms such as pain and fatigue are attracting increasing attention. Antidepressant treatment should be considered for patients meeting diagnostic criteria for depressive episode (ICD-10) *or major depressive episode* (DSM-IV). *Treatment choice depends on the concurrent symptom profile, the disease and treatment history, and patient preference. It should always target the most severe symptoms, ie, those that most endanger the patient and/or others.*

◆ *Suicidality and extreme malnutrition/dehydration are life-threatening conditions requiring priority acute treatment. Suicidality, whether passive (the feeling that life is no longer worth living) or active (ideation, planning, or attempted implementation), is generally an indication for inpatient treatment, in an intensive care unit if acute. Fast-acting benzodiazepines are indicated. Antidepressants that increase activation should be used with caution and the response closely monitored. Hospitalization is mandatory for extreme malnutrition/dehydration since force-feeding may be needed.*

◆ *Psychotic features, particularly delusions of guilt and nihilistic thinking, are a major threat to the patient and others. As such, they require immediate targeting, usually with antipsychotics (including benzodiazepines in the acute state) in an inpatient setting.*

◆ *Anhedonia, a core feature of depression, is a mandatory treatment target since the prolonged inability to experience pleasure substantially increases suicide risk. It requires antidepressants and/or psychotherapy on an inpatient or outpatient basis, depending on severity.*

◆ *Severe agitation stresses the patient and must be targeted with benzodiazepines and/or antipsychotics.*

◆ *Anxiety is common in depressive episodes and contributes to the suicidal phenotype. Panic disorder in particular increases the risk of suicidal behavior.*[1,2] *Depending on acuteness and severity, benzodiazepines and antidepressants are indicated in combination with psychotherapy.*

◆ *Rapid relief of sustained insomnia stress enhances mood and provides resources for recovery. Standard options are sedating antidepressants, eg, amitriptyline or mirtazapine, or antipsychotics and short-term benzodiazepines.*

Outside the well-recognized influence of demography, disease history, and somatic/psychiatric comorbidity, antidepressant response has not been clearly shown to differ with psychopathological symptom profile. However, evidence suggests that tricyclic antidepressants are more potent than selective serotonin reuptake inhibitors (SSRIs) in severely depressed inpatients.[3] *Indirect meta-analysis showed the dual-action serotonin-norepinephrine reuptake inhibitor venlafaxine, introduced in 1993, to be more effective than the SSRI fluoxetine.*[4] *Monoamine oxidase inhibitors may be preferable for atypical features, eg, mood reactivity, overeating and hypersomnia.*[5] *Electroconvulsive therapy is an option in life-threatening situations or when otherwise appropriate drugs are contraindicated. Depressive symptoms do not respond to treatment at the same rate or to the same degree. With some drugs, eg, the SSRI sertraline,*[6] *this can be explained by individual pharmacodynamics. Whether the order of symptom improvement is relevant to episode outcome is currently unknown. Recent review suggests that residual symptoms (eg, subthreshold depressive symptoms, cognitive impairment, and sexual dysfunction) influence long-term outcome: they increase the risk of relapse, impede the return to psychosocial and occupational functioning, favor chronification, and increase suicide risk.*[7] *As such, they are major targets of long-term treatment in depressive disorders. Thus, symptoms that are life-threatening to the patient and/or others must be the primary target of depressive episode treatment, bearing in mind that not all symptoms respond at the same rate or to the same degree. Residual symptoms are common and must not be overlooked in long-term treatment.*[8] ❐

REFERENCES

1. *Sareen J, Cox BJ, Afifi TO, et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults.* Arch Gen Psychiatry. *2005;62:1249-1257.*

2. *Weissman MM, Klerman GL, Markowitz JS, Ouellette R. Suicidal ideation and suicide attempts in panic disorder and attacks.* N Engl J Med. *1989;321:1209-1214.*

3. *Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability.* J Affect Disord. *2000;58:19-36.*

4. *Eckert L, Lancon C. Duloxetine compared with fluoxetine and venlafaxine: use of meta-regression analysis for indirect comparisons.* BMC Psychiatry. *2006;6:30.*

5. *Henkel V, Mergl R, Allgaier AK, Kohnen R, Moller HJ, Hegerl U. Treatment of depression with atypical features: a meta-analytic approach.* Psychiatry Res. *2006;141:89-101.*

6. *Boyer P, Tassin JP, Falissart B, Troy S. Sequential improvement of anxiety, depression and anhedonia with sertraline treatment in patients with major depression.* J Clin Pharm Ther. *2000;25:363-371.*

7. *Kennedy N, Foy K. The impact of residual symptoms on outcome of major depression.* Curr Psychiatry Rep. *2005;7:441-446.*

8. *Bauer M, Bschor T, Pfennig A, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care.* World J Biol Psychiatry. *2007;8:67-104.*

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Depression is a prevalent and devastating disorder with a complex etiology involving a variety of neurobiological and socioeconomic factors.[1] It is also multifaceted in its phenomenology, manifested in shifting constellations of symptoms and severities. High recurrence rates and comorbid anxiety often impair functional capacity and quality of life. Melancholia has been recognized since the fourth century BC. Its key symptoms were long regarded as the core of clinical depression, although they have recently been portrayed as aligned more closely with bipolar states.[2] Melancholic symptoms have classically been the primary target for antidepressants and electroconvulsive therapy. They show a significantly lower placebo response, and may also be less responsive to various forms of psychotherapy.[3] They have been widely tested using instruments such as the Beck Depression Inventory, via such items as sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, loss of interest, irritability, and sleep and appetite changes,[4] and the Mini International Neuropsychiatric Interview. A major obstacle when assessing the efficacy of antidepressants against their primary targets is the remarkably high placebo response rate in clinical trials. This has been ascribed to the intrinsic therapeutic effect of the intensive monitoring involved.[5] Placebo response is inversely related to depression severity, being more marked in the case of noncore symptoms or milder, nonmelancholic disease. Although no consistent difference has been found between melancholic and nonmelancholic patients, most studies record that only 20% to 30% of melancholic patients respond to placebo. Low mood reactivity is closely related to other core symptoms in melancholia, and may thus be regarded as the primary treatment target. In some studies, tricyclic antidepressants are more effective in this regard than selective serotonin reuptake inhibitors, but this is not a consistent finding.[3] Total remission should be the treatment target, as partial response carries a high risk of relapse. ❐

REFERENCES
1. *Lorant V, Croux C, Weich S, Deliege D, Mackenbach J, Ansseau M. Depression and socio-economic risk factors: 7-year longitudinal population study.* Br J Psychiatry. *2007; 190:293-298.*
2. *Akiskal HS, Akiskal KK. A mixed state core for melancholia: an exploration in history, art and clinical science.* Acta Psychiatr Scand. *2007:115(suppl 433):44-49.*
3. *Brown WA. Treatment response in melancholia.* Acta Psychiatr Scand. *2007;115(suppl 433):125-129.*
4. *Steer RA, Ball R, Ranieri WF, Beck AT. Dimensions of the Beck Depression Inventory-II in clinically depressed outpatients.* J Clin Psychol. *1999;55:117-128.*
5. *Posternak MA, Zimmerman M. Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials. Meta-analysis.* Br J Psychiatry. *2007;190:287-292.*

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Major depression, defined according to Diagnostic and Statistical Manual of Mental Disorders Fourth Revision (DSM-IV) *criteria, comprises at least five of the following nine symptoms: depressed mood; loss of interest or pleasure; weight loss; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue; feelings of worthlessness or guilt; difficulty to concentrate; and suicidal ideation.[1] These symptoms have been deemed most specific of the disorder and hence most useful for making valid and reliable diagnoses. Patients diagnosed with depression, however, have many other symptoms, in particular anxiety. This explains why scales designed to rate treatment response, eg, the Hamilton Rating Scale for Depression (HAMD), contain anxiety-related items. To aid differential diagnosis between depressive subtypes and anxiety disorders, studies have attempted to identify the core signs and symptoms of depression, eg, Parker's work on motor retardation[2] or the development of the Newcastle Scales.[3] However, without hard biological markers to validate symptom profiles derived from clinical studies, it is difficult to establish borders between depressive, anxiety and bipolar disorders, or even to identify the true or most important symptoms of depression. Few studies have addressed the effects of drugs on individual depressive symptoms, since the vast majority of clinical trials have used total rating scale scores as outcome variables. Analysis of the outcome of each and every item on a depression rating scale in a single trial would be subject to statistical limitations associated with the issue of multiple comparisons. Even when symptoms are clustered, comparisons are still too many for meaningful statistical analysis. Received wisdom holds that antidepressants only begin to act after 2 or more weeks, with the corollary that any earlier response is evidence of placebo rather than pharmacological effect.[4] Recent contrary data, however, suggest that improvement in major depression may occur much earlier, by the end of the first week.[5] This paradigm shift may encourage more studies on the sequential improvement of depressive symptoms in clinical trials. The therapeutic effects of antidepressants have been differentiated from those of placebo on the basis of the pattern of response over time rather than of individual symptom response.[4] An exception is the depressive subtype melancholia, where symptoms such as lack of reactivity, morning depres-*

sion, terminal insomnia, marked retardation, significant weight loss, and excessive guilt have been shown to predict poor placebo response.[6] In theory there is an urgent practical need to prioritize certain symptoms, in particular suicidal ideation. However, there is disputed evidence that antidepressants are associated with treatment-emergent suicidal ideation and suicide-related behavior, although not with completed suicide, in children, adolescents and adults; on this basis, current antidepressants may be ineffective for securing rapid control of suicidal ideation or suicide attempts.[7] A good case for prioritized treatment could also be made for any symptom whose initial improvement is associated with better subsequent outcome. The few studies of sequential improvement in depressive symptoms suggest that early decreases in anxiety—HAMD 17 anxiety-somatization factor and psychic anxiety—are associated with subsequently higher responder and remitter rates.[8-10] Interestingly, these findings are consistent with current practice in that the effect of antidepressants on anxiety symptoms is the main feature that doctors consider when choosing one drug over another.[11] Thus the main reason why bupropion is less prescribed than other second-generation antidepressants appears to be its lack of anxiolytic effect.[12] Insomnia often fails to respond to antidepressants in clinical trials and may even worsen.[13] Cotreatments targeted at insomnia have therefore been proposed to augment response, remission, and adherence.[14] Novel antidepressants such as agomelatine, which target underlying biorhythm disruption, are more effective in sleep disturbance and may have an important impact in the clinical management of major depression.[15] Antidepressants that differ in their mechanisms of action may differ in the degree and timing of their effects on individual symptoms. Thus, the first symptoms to respond to the norepinephrine reuptake inhibitor desipramine and the selective serotonin reuptake inhibitor paroxetine were psychomotor retardation and anxiety, respectively, while placebo showed no pattern of improvement in association with subsequent remission and response in a clinical trial.[16] In summary, limited evidence suggests that the symptom to be prioritized in the treatment of major depression is not one conventionally classified as depressive, but anxiety, in particular psychic anxiety. ❒

REFERENCES

1. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). *Washington, DC: American Psychiatric Association; 2005.*

2. *Parker G. Beyond major depression.* Psychol Med. *2005;35:467-474.*

3. *Maier W, Philipp M, Buller R, Schlegel S. Reliability and validity of the Newcastle Scales in relation to ICD-9-classification.* Acta Psychiatr Scand. *1987;76:619-627.*

4. *Stewart JW, Quitkin FM, McGrath PJ, et al. Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo.* Arch Gen Psychiatry. *1998;55:334-343.*

5. *Tylee A, Walters P. Onset of action of antidepressants.* BMJ. *2007;334:911-922.*

6. *Brown WA. Treatment response in melancholia.* Acta Psychiatr Scand Suppl. *2007;433:125-129.*

7. *Reith DM, Edmonds L. Assessing the role of drugs in suicidal ideation and suicidality.* CNS Drugs. *2007;21:463-472.*

8. *Farabaugh A, Mischoulon D, Fava M, et al. The relationship between early changes in the HAMD-17 anxiety/somatization factor items and treatment outcome among depressed outpatients.* Int Clin Psychopharmacol. *2005;20:87-91.*

9. *Davidson JR, Meoni P, Haudiquet V, Cantillon M, Hackett D. Achieving remission with venlafaxine and fluoxetine in major depression: its relationship to anxiety symptoms.* Depress Anxiety. *2002;16:4-13.*

10. *Trivedi MH, Morris DW, Grannemann BD, Mahadi S. Symptom clusters as predictors of late response to antidepressant treatment.* J Clin Psychiatry. *2005;66:1064-1070.*

11. *Zimmerman M, Posternak M, Friedman M, et al. Which factors influence psychiatrists' selection of antidepressants?* Am J Psychiatry. *2004;161:1285-1289.*

12. *Zimmerman M, Posternak MA, Attiullah N, et al. Why isn't bupropion the most frequently prescribed antidepressant?* J Clin Psychiatry. *2005;66:603-610.*

13. *Wilson S, Argyropoulos S. Antidepressants and sleep: a qualitative review of the literature.* Drugs. *2005;65:927-947.*

14. *Fava M, Rush AJ. Current status of augmentation and combination treatments for major depressive disorder: a literature review and a proposal for a novel approach to improve practice.* Psychother Psychosom. *2006;75:139-153.*

15. *Kupfer DJ. Depression and associated sleep disturbances: patient benefits with agomelatine.* Eur Neuropsychopharmacol. *2006;16(suppl 5):S639-S643.*

16. *Katz MM, Tekell JL, Bowden CL, et al. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression.* Neuropsychopharmacology. *2004;29:566-579.*

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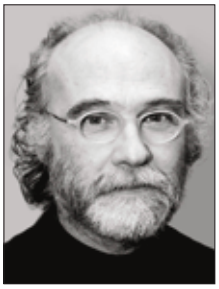

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Why should we need to prioritize target symptoms in the treatment of depression? The question presupposes that some symptoms are more life-threatening or significant than others. Our first task is therefore to hierarchize symptoms along these lines. Depression is commonly viewed as comprising core symptoms (depressed mood and anhedonia) associated with three (emotional, physical, and cognitive) symptom clusters. However, this view is unsupported by any pathophysiological mechanism or mechanisms common to all forms of depression. Until such mechanisms are identified, we have no option but to base our definition of depression, and our resulting treatment options, on the phenomenology of the disorder. If we now analyze the structure of these phenomenological symptom clusters, can we hierarchize certain symptoms in terms of risk or their potential impact on other symptoms, such that successful treatment of one symptom could encompass a spectrum of others? In the absence of hard physical data, we can only base our answer on clinical experience. What that experience teaches us is that if we first treat the core symptoms, we achieve global clinical improvement. This suggests that these symptoms, in some unknown way, play a central role in the pathophysiology of the disorder. They must therefore be considered as treatment priorities. Clinical experience also teaches us that cognitive symptoms are important for informing treatment strategy in depression. They respond quite independently from other symptom clusters. When patients improve in their mood and associated physical symptoms, they often retain the same cognitive disturbance as in the acute phase of the disorder. Clinical experience teaches us that treating cognitive symptoms first has practically no effect on relieving depression, except in its milder forms. The implication is that we must first treat the core symptoms, at least in severe depression, if we are to achieve any global improvement that allows intervention against cognitive symptoms. The conclusion informed by clinical experience is that the core symptoms of depressed mood and anhedonia must be treated first, at least in severe depression, and that cognitive symptoms should be targeted in the second phase of treatment. Clinical experience has shown that improvement in depressive mood is a precondition for obtaining significant benefit from cognitive remediation therapy. ❐

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Insomnia is both a symptom and cause of depression. It may even be the worst symptom: to lie awake unable to rest while a prey to pessimistic thoughts is torment. Insomnia is a proven marker for increased suicidality. We recently showed a correlation between sleep disturbance, in particular nightmares, and suicidality and suicide attempts.[1] Sleep disturbance in depression—sleep-onset insomnia, frequent nocturnal awakening, and early morning awakening—reflects underlying circadian dysregulation, mediated by the suprachiasmatic pacemaker. Dysfunctional circadian input may also influence monoaminergic activity, lowering serotonin activity and melatonin levels, with effects on timekeeping and hence sleep. Stress has a major role in the development of depression. Some degree of stress is tolerable, but overload is harmful. Disturbed sleep is the best clinical sign of excessive stress. Stress can be tolerated as long as sleep function is normal. But insomnia is evidence of an overactive hypothalamo-pituitary-adrenal axis. The regulatory peptide corticotropin-releasing factor not only influences the release of adrenocorticotropic hormone, but also the limbic system, inhibiting delta sleep. This dysregulation may also feed back onto the circadian pacemaker. Disruptions in the biological clock mechanism may be both a cause and a consequence of depression. Insomnia is itself a risk factor for the development of depression as shown in several epidemiological studies[2] and borne out in clinical experience. Antidepressants that relieve certain symptoms without correcting sleep disturbance will not achieve a significant response and will incur a high rate of relapse. Patients feel better if their sleep disturbance improves early during treatment. They are otherwise likely to feel worse. The risk that selective serotonin reuptake inhibitors may initially worsen sleep should be counteracted by the addition of hypnotics. The ideal antidepressant is a drug that rapidly improves sleep and resets the circadian system. Sleep disturbance should thus be the primary target in treating depression. This recommendation may appear to conflict with the rapidly positive effect that sleep deprivation may have in melancholia. However, sleep deprivation works by resetting the disrupted circadian system. Other methods that act on the circadian pacemaker can be equally effective. In order to improve sleep as a basis for mood reversal, there are thus sound scientific as well as clinical grounds for prioritizing circadian rhythm in the treatment of depression. ❐

REFERENCES
1. *Sjostrom N, Waern M, Hetta J. Sleep disturbances in relation to suicidality in suicide attempters.* Sleep. *2007;30: 91-95.*
2. *Mallon L, Broman JE, Hetta J. Relations between insomnia, depression and mortality; a twelve year follow up study.* Int Psychogeriatr. *2000;12:295-306.*

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I would nominate as the priority treatment target one of the so-called core symptoms, such as depressed mood, lack of interest, lack of energy, guilt, psychic anxiety, or somatic anxiety.[1,2] This is because improvement in core symptoms tends to benefit other symptoms and eventually lead to full remission. However, it is difficult to identify the core symptom(s) in an individual patient because depression is heterogeneous in its pathogenesis. Since psychiatric symptoms can be clinically differentiated at multiple levels, phenomenological similarity does not reflect similarity of origin or structure.[3] A further complication is that the symptoms that appear as priorities for the patient may not be those that require priority treatment: our (unpublished) observations indicate that the Beck Depression Inventory (BDI) is less sensitive than clinician rating at identifying responders and remitters, especially in the early treatment period. Thus, at present, clinicians are obliged to choose a core symptom as their priority treatment target because antidepressants have shown no specific differences in their mechanism of action on target symptoms.[2]

Is the order of symptom improvement a relevant clinical factor?

The order of symptom response to antidepressants appears to depend on the drug receptor profile. For example, duloxetine, a serotonin-norepinephrine reuptake inhibitor, improved depressed mood, guilt, suicidal ideation, work/activity, and anxiety in the first week, motor retardation in the second week, motor retardation and hypochondriasis in the third week, and general somatic symptoms, insomnia, and insight after the fifth week.[4] With desipramine, a tricyclic antidepressant that inhibits the reuptake of norepinephrine, early response was shown by motor retardation and depressed mood, while with the selective serotonin reuptake inhibitor paroxetine, anxiety, depressed mood, and distressed expression were the first to improve.[5] As no biological markers for antidepressant treatment have been found and as current practice relies on rating scales, assessment of a patient's treatment has to be based on improvement in the core symptoms, especially during the early treatment period.[1,2,5] Clinically, the degree of symptom response is more relevant than its order, although there does appear to be a characteristic order of symptom response to antidepressants. Residual symptoms are less sensitive to antidepressants and may be more clinically relevant in that they heighten the risk of relapse.[6] Our (unpublished) finding in nonpsychotic major depressive disorder is that the negative self-concept factor in the BDI (items such as feeling of guilt, sense of punishment, self-hate, and self-accusation) is relatively less sensitive to change than observer ratings. This factor may therefore be clinically relevant in treating depression.

Is the placebo effect more important for some noncore symptoms?

Recent neurobiological studies suggest that placebo effects are not as simple as previously thought and that they may be clinically relevant by enhancing the effect of specific treatments.[7,8] In the hierarchy of classes of personal illness model proposed in 1975 by Foulds and Bedford,[9] depression occupies a lower hierarchical class. Endogenous depression, on the other hand, especially melancholia and psychotic depression, appears more biologically determined,[10] and does not occupy a lower hierarchical class. Studies from the 1970s suggest that the frequency of placebo effects increases from anxiety disorder, through depressive disorder, to schizophrenia. If we assume that core symptoms are the final common pathway in the pathogenesis of depression and that placebo effects are salient solutions to given stimuli in an individual,[7,8] the noncore symptoms that could be classified in the lowest hierarchical class[9] may be more likely to respond via a placebo effect. ❐

REFERENCES

1. *Evans KR, Sills T, DeBrota DJ, Gelwicks S, Engelhardt N, Santor D. An item response analysis of the Hamilton Depression Rating Scale using shared data from two pharmaceutical companies.* J Psychiatr Res. *2004;38:275-284.*

2. *Nelson JC, Portera L, Leon AC. Assessment of outcome in depression.* J Psychopharmacol. *2006;20(4 suppl):47-53.*

3. *Markova IS, Berrios GE. Mental symptoms: are they similar phenomena? The problem of symptom heterogeneity.* Psychopathology. *1995;28:147-157.*

4. *Hirschfeld RM, Mallinckrodt C, Lee TC, Detke MJ. Time course of depression-symptom improvement during treatment with duloxetine.* Depress Anxiety. *2005;21:170-177.*

5. *Katz MM, Tekell JL, Bowden CL, et al. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression.* Neuropsychopharmacology. *2004; 29:566-579.*

6. *Menza M, Marin H, Opper RS. Residual symptoms in depression: can treatment be symptom-specific?* J Clin Psychiatry. *2003;64:516-523.*

7. *de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease.* Science. *2001;293:1164-1166.*

8. *Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect.* J Neurosci. *2005;25:10390-10402.*

9. *Foulds GA, Bedford A. Hierarchy of classes of personal illness.* Psychol Med. *1975;5:181-192.*

10. *Kaestner F, Hettich M, Peters M, et al. Different activation patterns of proinflammatory cytokines in melancholic and non-melancholic major depression are associated with HPA axis activity.* J Affect Disord. *2005;87:305-311.*

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Prioritizing symptoms in order to optimize treatment strategy is a crucial and complex issue in managing major depression. Depressed patients often overemphasize specific symptoms (eg, cognitive disturbance, loss of interest, sleep difficulties). This may be useful in establishing the diagnosis, but it can be misleading in informing treatment choice. Patients may stress certain persistent symptoms (eg, insomnia, somatic symptoms) at the expense of others that appear less severe, but are more meaningful in terms of drug response. In addition, there are specific populations, such as the elderly, with their own clinical patterns, which tend to be more severe and to carry a poorer prognosis than in nonelderly adult depressives:[1] elderly depressives have more somatization, hypochondriasis, anxiety/retardation, and delusionality, but less guilt, loss of libido, and family history of depression, as well as a less predictable therapeutic response; despite much lower medication doses, side effects are also more troublesome in this age group.[2] Given the symptom heterogeneity, it is mandatory to use standardized rating scales, such as the Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale, for qualitative and quantitative assessment and for optimizing intervention. In choosing an initial treatment modality, the first consideration is the setting: the choice between hospitalization and outpatient care depends on suicidal ideation and symptom severity, in particular the presence or absence of psychotic features. The second consideration is the choice between pharmacology and electroconvulsive therapy, and if pharmacology, the choice of agent. Life-threatening situations must be addressed as rapidly as possible for the safety of patients and those around them. Less urgently, in order to minimize the development of antidepressant resistance, it is important to consider the duration of certain symptoms and of untreated illness in patients experiencing a first or recurrent depressive episode.[3] Current pharmacological classes of antidepressants allow clinicians to choose the most appropriate agent in light of specific symptom patterns. Certain drugs show symptom specificity. Serotonin norepinephrine reuptake inhibitors (SNRIs), for example, are most effective in cognitive disturbance and/or somatic complaints such as pain.[4] Mirtazapine and trazodone may be particularly useful in sleep disturbance,[5] along with melatonergic agents such as agomelatine.[6] The holy grail of pharmacotherapy is to develop rapid-onset agents that accelerate symptom response and remission. Recent examples include escitalopram, a selective serotonin reuptake inhibitor (SSRI), and the SNRIs venlafaxine and duloxetine. However, rapid onset of effect is not the only factor to consider in a treatment plan, even in severe disease. Tolerability is a critical consideration when efficacy depends on treatment compliance. Therapeutic strategy must therefore be based on a combination of disease factors (symptom severity, profile, and duration, and pattern of recurrence[7]) and pharmacotherapeutic factors (efficacy, tolerability, and time to effect). In prioritizing treatment targets, consideration should be given to the most urgent symptoms, especially if somatic, suicidal, and/or psychotic, followed by the patient's own symptom hierarchy. But the restoration of the fundamental biological rhythms governing sleep, appetite, and other functions must never be neglected. Biorhythm normalization is essential for breaking the vicious cycle of dysregulated affective brain circuits and dysfunctional hypothalamus that can underlie the core biological symptoms of depression. Dysfunctional biorhythms maintain cortical and subcortical circuit imbalance and vice-versa. Drugs designed to normalize biorhythm disruption may be the most promising additions to the pharmaceutical armamentarium against major depression. ❐

REFERENCES

1. *Ruegg RG, Zisook S, Swerdlow NR. Depression in the aged. An overview.* Psychiatr Clin North Am. *1988;11:83-99.*
2. *Altamura AC, Mauri MC, Rudas N, et al. Clinical activity and tolerability of trazodone, mianserin, and amitriptyline in elderly subjects with major depression: a controlled multicenter trial.* Clin Neuropharmacol. *1989;12:S25-S33;S34-S37.*
3. *Altamura AC, Dell'Osso B, Mundo E, Dell'Osso L. Duration of untreated illness in major depressive disorder: a naturalistic study.* Int J Clin Pract. *In press.*
4. *Perahia DG, Pritchett YL, Desaiah D, Raskin J. Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect?* Int Clin Psychopharmacol. *2006;21:311-317.*
5. *Thase ME. Antidepressant treatment of the depressed patient with insomnia.* J Clin Psychiatry. *1999;60(suppl 17): 28-31; discussion 46-48.*
6. *Kupfer DJ. Depression and associated sleep disturbances: patient benefits with agomelatine.* Eur Neuropsychopharmacol. *2006;16(suppl 5):S639-S643.*
7. *Angst J, Gamma A, Pezawas L, et al. Parsing the clinical phenotype of depression: the need to integrate brief depressive episodes.* Acta Psychiatr Scand. *2007;115:221-228.*

CORE SYMPTOMS OF DEPRESSION IN CLINICAL PRACTICE

Interview with S. Montgomery, United Kingdom

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What is the easiest way to assess core symptoms of depression in clinical practice?

Depression is a serious disorder that is underrecognized and undertreated. A large-scale survey carried out in European countries showed that in a cohort of 78 000 adults in which 17% were suffering from depression, 69% were not receiving medical treatment, and in those who were receiving treatment only 7.1% of patients with major depressive disorder (MDD) received an antidepressant.[1] In primary care, where depressed patients form a substantial proportion of the attendees, both patient-related and physician-related factors contribute to the frequent failure to detect or acknowledge the presence of depression. Patients may not mention depressive symptoms as they do not recognize depression in themselves, or they may perceive depression as having a low priority for general practitioners, or they may have a perception that antidepressant therapies have poor efficacy or have unwanted side effects. The physician, who can be constrained for time, may have poor recognition of depressive illness, may overdiagnose physical complaints that are manifestations of depression, or may interpret depressive symptoms as "understandable" reactions to circumstances. Patients and physicians alike are affected by the baleful influence of negative media comment and the stigma attached to mental health problems.

Diagnosing depression in clinical practice therefore requires that the physician elicit answers to specific questions in much the same way that the diagnosis of hypertension or diabetes requires intrusive tests. Patients with depression often present complaining of poor sleep, anxiety, and loss of energy and where these symptoms are present the patient should be closely questioned about the other core symptoms of depression. With depression, poor sleep is a good marker of evolving disorder and is one of the most frequent patient complaints that should draw the attention of the vigilant physician to probe further.

There is general agreement that the symptoms that form the basis of a diagnosis of MDD are the core symptoms of depression. These core symptoms are considered to be those that occur most frequently and increase in severity with increasing levels of severity of the disorder. The large number of studies in the extensive and rich literature on antidepressant treatments has shown consistency in the identification of the core symptoms of depression, which are part of the diagnostic process and which are used to measure severity of depression.

What are the main diagnostic criteria that can be the target for antidepressants?

The *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)*[2] diagnostic criteria set out a list of symptoms that have to be probed before a diagnosis of MDD can be made, with the requirement that a

Depression is serious, underrecognized and undertreated. A survey in 78 000 European adults demonstrated its presence in 17%, of whom 69% were untreated; only 7.1% of those with major depressive disorder were receiving an antidepressant. Both patient and physician factors are responsible for this failure to detect and treat depression in primary care. Negative media comment has a baleful influence and stigma remains attached to mental disorders. Yet depression can be diagnosed by eliciting answers to specific questions, much like hypertension or diabetes, and just as reliably and rapidly, even over the telephone. Physicians must be alert to complaints of poor sleep, anxiety and loss of energy. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) *requires depressed mood or loss of interest to have been associated for at least 2 weeks at a distressing or dysfunctional level with at least five core symptoms (appetite disturbance, sleep disturbance, psychomotor disturbance, fatigue or low energy, feelings of worthlessness or guilt, reduced concentration, and suicidal thoughts or attempts). There is substantial agreement between these items and the Montgomery & Asberg Depression Rating Scale, despite the radically different methods of construction involved. Treatment response is assessed using the same core items as for diagnosis. Effective treatment is defined by multi-item improvement sustained for 6 to 8 weeks. The fact that placebo response meets this definition in some patients complicates the conduct of clinical trials and should alert primary care practitioners to the psychotherapeutic benefit of constant evaluation and the reassurance inherent in sympathetic follow-up.*

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patient has to suffer from depressed mood or loss of interest with at least 5 other symptoms from the list. These core symptoms are depressed mood, loss of interest, appetite disturbance, sleep disturbance, psychomotor disturbance, fatigue or low energy, feelings of worthlessness or guilt, reduced concentration, and suicidal thoughts or attempts. There is substantial agreement between items identified in *DSM-IV* and the Montgomery & Asberg Depression Rating Scale (MADRS),[3] a scale for the assessment of severity of depression. This is of particular note given the different construction methods used for the two instruments. The MADRS was constructed, based on data in the field, as a scale sensitive to change with treatment, whereas the *DSM-IV* criteria were based on the consensus of opinion from a committee of experts as to which were the most relevant symptoms of depression.

The core symptoms of depression were identified for the MADRS on the basis of frequency (present in at least 70% of the test population), sensitivity to changes with treatment, and the items had also to be well understood by people from different cultures. The preliminary identification of the most frequently occurring items found that two items, worrying over trifles and observed muscular tension, while occurring frequently, were not in the first rank of sensitivity to change. Two items, reduced sleep and reduced appetite, were marginally less frequent, but were more sensitive to change. The final selection of 10 items based on sensitivity and frequency, which represent the core symptoms, were sadness, both observed and reported, inability to feel, inner tension, suicidal thoughts, lassitude, concentration difficulties, reduced sleep, reduced appetite, and pessimistic thoughts. The results of two different methods of construction arrived at very similar conclusions on the core symptoms of depression, with one item, inner tension, which was both frequent and sensitive, occurring in the MADRS, but not the *DSM-IV*.

To diagnose depression, a range of core symptoms needs to be elicited; to track the improvement in the disorder it is obviously necessary to assess change in the same symptoms that established the diagnosis. For a treatment of depression to be considered effective improvement on these core symptoms would be expected. In general, treatments that are effective in depression have been able to show efficacy, as measured by a reduction of a composite score covering the core features of depression.

Do different antidepressant treatments (pharmacological, sleep deprivation, etc) act on different core symptoms?

Treatment effective on one symptom alone, eg, hypnotics, which improve sleep latency (getting off to sleep), have not been shown to be effective as antidepressants because they lack the ability to produce a response on the other core symptoms. Similarly, benzodiazepines, which have been shown to be effective in treating anxiety symptoms and sleep disturbance, are not looked upon as antidepressants in their own right. The idea that a treatment may be focused on a single core symptom is not regarded as sufficient to establish efficacy as an antidepressant. Unless there are significantly more responders treated with an antidepressant based on a composite score compared with placebo, experts do not consider that treatment to be effective. In general, treatments recognized as effective in MDD seem to have an overall beneficial effect on most of the symptoms.

A treatment is also only regarded as being effective in MDD if the beneficial effects are sustained for a period 6 to 8 weeks. For this reason, sleep deprivation, which has been shown in some studies to have some beneficial transient effect on a range of symptoms for a few days, cannot be regarded as adequate treatment of depression.

Placebo has been shown to have an effect on core symptoms that may be sustained for 6 to 8 weeks in some patients, reflecting to some extent the fluctuating nature of depression, with a proportion of patients showing spontaneous improvement. This apparent efficacy also reflects the beneficial psychotherapeutic effects of constant evaluation of the depression and the reassurance inherent in attending a clinic under sympathetic supervision. To qualify as an antidepressant, a treatment of depression is required to be more effective than placebo given under these reassuring conditions and this is the rationale for conducting carefully managed randomly assigned placebo-controlled investigations.

As depression improves, the symptoms tend to improve together so that any treatment of depression, if it is effective, will have some beneficial effect on all of the core symptoms. However, many antidepressants have side effects that impact negatively on some of the core symptoms. Selective serotonin and norepinephrine reuptake inhibitors (SSRIs, SNRIs) produce nausea and problems with appetite, increased nervousness, or agitation as part of their pharmaceutical action, and these effects may impact on anxiety symptoms of depression or impair sleep. SSRIs and SNRIs have been shown to impair sexual function, and some antidepressants with prolonged antihistaminic effects, although they improve sleep, do so at the expense of day time concentration and psychomotor function. Tricyclic antidepressants (TCAs), which have anticholinergic and histaminergic effects, reduce the ability to concentrate, function, drive a car, or operate machinery.

Scales, interviews, self- or hetero-evaluation—which is the most appropriate method?

It is rare for patients to volunteer the core symptoms. They need to be systematically evaluated. This is most easily done using a well-known depression rating scale. In Norway, for example, physicians are reimbursed for completing an MADRS interview as an incentive to recognize the presence of depression and therefore encourage its treatment. Physicians may have an understandable resistance to asking systematically after core symptoms, a reluctance that may be driven partly by the stigma attaching to the disorder. They are also often unaware of how quickly core symptoms may be assessed. The presence or absence of the core symptoms is easy to establish with very few questions. The quantification of severity may take a little longer.

The Hamilton rating scale[4] is very widely used for assessing depression, though it has the disadvantage of containing some items covering symptoms and behaviors, which, though part of depression, are uncommon and relatively insensitive to change. The scale has been subjected to several revisions by other investigators, but whether you use the 17-, 21-, 24-, or 28-item version, there are too many redundant items that are insensitive to change. There are also self-rating scales derived from the Hamilton scale, though these tend to be cumbersome and have not been shown to be particularly useful in routine practice.

Some scales to measure depression have deliberately excluded certain core symptoms such as poor appetite or poor sleep. For example, the Bech Melancholia Scale[5] excludes sleep disturbance despite the fact that early morning wakening is a well-recognized symptom of melancholia. The exclusion of disturbed sleep and disturbed appetite may tend to make

those antidepressants that disrupt sleep and appetite appear better than they really are. A good antidepressant should be able to improve all the symptoms of depression rather than just selected items.

Self-rating scales have been used and have their place provided that scales cover the core symptoms and are easily understood. Their use is obviously limited in patients who have difficulty understanding or who are severely ill. They have no place in assessing depression in patients who are illiterate.

Although it is more reliable to interview a patient face to face, there are many occasions when this may not be possible. It is quite possible to assess the core symptoms of depression in telephone interviews, either in a direct conversation with the patient or indirectly via a voice interactive computer-generated interview. There may be some difficulty in assessing certain behavioral symptoms, but these interviews have nevertheless been shown to be reliable and able to reflect response or deterioration. The voice interactive system has the advantage of not being prone to the bias of the interviewer; moreover, some sensitive information may be more readily obtained by this means than in the face-to-face interview where a patient is aware of the stigma associated with mental illness. Normal management of a patient should include regular monitoring of progress, but the need to come to the surgery for this assessment is uneconomic and inefficient and may contribute to discontinuation from therapy.

Would it be more relevant for GPs to rely on core symptoms only for the diagnosis and the assessment of recovery of depression?

In order to diagnose MDD according to the *DSM-IV,* or for that matter to diagnose depressive illness following the International Statistical Classification of Diseases and Health-Related Problems, 10th Revision (ICD-10) system, it is necessary to check on all of the core diagnostic symptoms. Depression is a disorder where the sufferer may have some symptoms and not others, and it is for this reason that the formulation of the diagnostic system is that as well as depressed mood or loss of interest there should be evidence of the presence a total of 5 out of the 9 core symptoms at a distressing or dysfunctional level for at least 2 weeks.

Monitoring the progress of the depressed patients will require the tracking of changes in the severity of these core symptoms in terms, and it would be unwise to cut corners and ignore any of them. The aim of treatment is not just to achieve a response with reduction in the severity of symptoms, but also to treat the depressed individual adequately to achieve remission, which is compatible with the recovered state. Remission is mostly defined by a low level of symptoms measured on the standard rating scales with, for example a cutoff score of 11 or less on the MADRS or 7 or less on the Hamilton scale. It would be difficult to justify examining a truncated list of core symptoms that might overlook, for example, worsening of sleep, appetite or even of suicidal thoughts. It is safer and better practice of course to concentrate on the core symptoms identified on the *DSM-IV* diagnostic system or on the MADRS to make sure that these symptoms have resolved satisfactorily and to check on the scores on the scales to be able to justify the status of remission.

Remission in an important goal since it is at this point that long-term treatment begins. The aim of long-term treatment is to consolidate remission and prevent relapse in a period of continuation treatment in all patients, and to prevent recurrence in those with recurrent depression. It is necessary, in treating depression, whether in a primary care or a specialist setting, to pay assiduous attention to checking on all these core symptoms for adequate monitoring of response, remission, and, most importantly, sustained remission. ❐

REFERENCES

1. Lepine JP, Gastpar M, Mendlewicz J, Tylee A. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). *Int Clin Psychopharmacol.* 1997;12:19-30.

2. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.* Washington, DC: American Psychiatric Association; 1994.

3. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.

4. Hamilton M. Development of rating scale for primary depressive illness. *Br J Soc Clin Psychol.* 1967; 6:278-296.

5. Bech P, Allerup P, Gram LF, et al. The Diagnostic Melancholia Scale (DMS): dimensions of endogenous and reactive depression with relationship to the Newcastle Scales. *J Affect Disord.* 1988;14:161-170.

SYMPTÔMES MAJEURS DE LA DÉPRESSION EN PRATIQUE CLINIQUE

La dépression est une affection grave, sous-évaluée et sous-traitée. Une étude menée chez 78 000 adultes européens a mis en évidence l'existence d'une dépression chez 17 % des sujets, dont 69 % n'étaient pas traités, alors que seuls 7 % de ceux qui avaient un trouble dépressif majeur recevaient un antidépresseur. Cet échec pour détecter et traiter la dépression dans la prise en charge primaire est dû à des facteurs propres à la fois au patient et au médecin. S'y ajoute l'influence néfaste des commentaires péjoratifs des médias et de l'aura négative dont est toujours entachée la maladie mentale. Pourtant la dépression peut être diagnostiquée de façon fiable et rapide, même par téléphone, par la réponse à des questions spécifiques, comme cela se fait pour l'hypertension ou le diabète. Les médecins doivent être attentifs aux plaintes concernant un mauvais sommeil, une anxiété ou une perte d'énergie. Le DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) *exige la présence depuis au moins 2 semaines d'une humeur dépressive ou d'une perte d'intérêt atteignant un degré pénible ou handicapant conjointement à celle d'au moins cinq symptômes majeurs (troubles de l'appétit, troubles du sommeil, troubles psychomoteurs, fatigue ou baisse d'énergie, sensation de dévalorisation ou de culpabilité, baisse de concentration et idées ou gestes suicidaires). Ces items et l'échelle de dépression de Montgomery et Asberg sont tout à fait concordants, malgré des méthodes d'interprétation radicalement différentes. La réponse au traitement est évaluée au moyen des mêmes items majeurs utilisés pour le diagnostic. L'efficacité du traitement est définie par l'amélioration prolongée pendant 6 à 8 semaines des symptômes majeurs. La réponse au placebo remplissant également cette définition chez certains patients, la conduite des études cliniques s'en trouve compliquée, ce qui devrait attirer l'attention des médecins généralistes sur l'intérêt psychothérapeutique d'une évaluation constante et du réconfort procuré par un suivi bienveillant.*

A FUNCTIONAL BRAIN IMAGING PERSPECTIVE IN DEPRESSION

by P. Fossati, France

Functional and structural neuroimaging offers an unrivalled window onto the neuroanatomy of depression. Positron emission tomography (PET) studies of cerebral blood flow and glucose metabolism have consistently characterized major depressive disorder, whether primary or associated with specific or diffuse brain lesions, as a system-level illness affecting discrete, but functionally integrated cortical, subcortical, and limbic pathways.[1,2]

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Resting state studies

Brain metabolism and regional blood flow have been measured in depressed subjects at rest (ie, in the absence of specifically oriented mental activity), in ventral and dorsal prefrontal cortex, anterior cingulate, basal ganglia, amygdala, and hippocampus. The best-replicated behavioral correlate of a resting state abnormality is that of an inverse relationship between prefrontal activity and depression severity.[3] Specific neural network changes are associated with symptomatic dimensions of depression that have been grouped into affective, circadian-somatic, cognitive, and motor behavioral subsystems to allow easier evaluation of the mechanisms mediating variation in normal behavior domains. Dorsolateral prefrontal cortex (DLPFC) activity has been linked both to psychomotor speed and to executive functions[4] that include a set of cognitive processes engaged in the integration of multimodal sensory input, the generation of multiple response alternatives, planning abilities, and self-evaluation.[5,6]

Parietal and parahippocampal activity has been associated with anxiety,[7] and medial frontal and cingulate activity with cognitive performance and emotional bias.[8,9] A more complex ventral-dorsal segregation of frontal lobe function has also been described, with a positive correlation between ventral prefrontal activity and anxiety/tension, and a negative correlation between dorsolateral activity and psychomotor and cognitive slowing.[10]

Cognitive activation studies: emotional processing

Studies of resting state patterns have been complemented by activation experiments using PET or functional magnetic resonance imaging (fMRI) of specific cognitive and emotional processes in healthy volunteers and depressed patients. Emotional processing in depression is characterized by

SELECTED ABBREVIATIONS AND ACRONYMS

ACC	anterior cingulate cortex
DLPFC	dorsolateral prefrontal cortex 1
fMRI	functional magnetic resonance imaging
PET	positron emission tomography
SSRI	selective serotonin reuptake inhibitor

Functional brain imaging studies suggest that depression is a system-level disorder affecting discrete, but functionally linked, corticolimbic structures with abnormalities in the anterior cingulate, lateral and medial prefrontal cortex, amygdala, and hippocampus. Within this circuitry, abnormal corticolimbic interactions underlie the characteristic cognitive deficits and emotional impairment. Depression involves a cognitive bias toward processing negative emotional information congruent with the patient's mood and worries, possibly reflecting prolonged involuntary processing of emotional stimuli and impaired modulation of emotional responses to negative stimuli. Antidepressant treatment, whether with drugs or psychotherapy, may help the brain to restore cognitive and emotional homeostasis by improving connectivity in dysfunctional corticolimbic pathways. Pretreatment increases in rostral anterior cingulate and amygdalar activity predict clinical response to antidepressant drugs. By combining structural and functional investigations, brain imaging studies may help to generate novel antidepressant treatments that regulate structural and functional plasticity within the neural network regulating mood and affective behavior.

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Keywords: *brain; depression; functional magnetic resonance imaging; positron emission tomography; antidepressant*

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bias toward the processing of negative stimuli,[11] via mechanisms that remain unelucidated. Mood disorders may be associated with abnormalities in the way emotional stimuli are perceived, interpreted, and stored in memory. Depressed patients allocated more attention to sad than happy faces in a dot-probe task, but because they showed no similar bias toward other negative stimuli, such as angry faces, they appeared not to have a general problem with negative emotional stimuli per se.[12] They interpret emotionally neutral faces as sad,[13] have a better memory for negative stimuli, including words and pictures, and show diminished responsiveness to positive stimuli.

Several fMRI studies have evaluated the neural correlates of impaired emotional processing in depression with special focus on the amygdala, a medial temporal structure involved in processing facial expression, assigning valence and arousal to stimuli, and generating emotional responses to stimuli. Presentation of sad faces prompted an increase in amygdalar and ventral striatal activity which was attenuated by treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine for 8 weeks.[14] Amygdalar responses to negative emotional words were abnormally sustained in depressed patients compared to normal controls.[15] This could be an important neural correlate of rumination, a common clinical feature of major depressive episode. Other fMRI studies in depression using emotional words have shown reduced activation in frontotemporal and limbic regions in response to positive stimuli.[16,17]

Depression and cognitive resources

Depression may not result only from selective regional or pathway dysfunction, but also from failure of the remaining systems to maintain emotional homeostasis in times of increased cognitive demand.[2] Cognitive or information-processing resources are not unlimited, even in normal subjects, and mental operations differ in their attentional or cognitive requirements. Automatic processes run in parallel, unrestricted by short-term memory capacity, and require little or no cognitive effort, but they require practice to develop, and are restricted to situations in which a given stimulus consistently involves the same response. Controlled processes, on the other hand, run in sequence, are restricted by short-term memory capacity, are effortful, and improve with minimal practice.[18]

Depression interferes with effortful cognitive processes, leaving automatic processes intact in several domains, eg, learning, memory, problem-solving, reading, and speed processing.[19] The effortful-deficit hypothesis in depression predicts impairment in actions requiring attentional and executive resources such as complex goal-directed behaviors. We suggest that deficits in depressed patients performing an effortful task are preceded by increasing effort to maintain a high performance level. Progressive exhaustion of cognitive resources precedes the deficits. Cognitive resource depletion is the end product of the failure by depressed patients to constantly adapt to cognitive and emotional demands. Thus testing depressed patients with a cognitive task they can perform is more important than demonstrating deficit in a task they cannot perform because how they are doing is more informative for understanding the pathophysiology of depression than what they are doing.[20] Recent behavioral and fMRI data support this hypothesis. Depressed patients with anhedonic features showed deficits in continuous attentional tasks compared to depressed patients with impulsive features.[20] These deficits appeared progressively during the task, displaying a time-on-task effect consistent with previous findings in normal anhedonic subjects, and suggesting that anhedonia trait and state are associated with a reduced capacity to sustain cognitive effort.[21]

In a recent fMRI study, we compared 10 depressed subjects and 10 normal controls in a verbal *n*-back working memory task that required the *n* stimuli to be maintained and updated each time a new stimulus occurred.[22] We manipulated the working memory load across the experiment (1,2,3-back) to increase cognitive demands. Having deliberately selected depressed patients who performed normally on the *n*-back task, we found no intergroup difference in either performance or reaction times at each level of complexity: both groups showed bilateral activation of the DLPFC (Broca area [BA] 9/46), premotor and supplementary motor areas (BA 6/8), Broca's area, dorsal anterior cingulate cortex (ACC), and parietal cortex. Task complexity modulated activation in these regions. Depressed patients showed greater DLPFC and dorsal ACC activation in the *n*-back neural network than normal controls. Of the three fMRI studies that have since used an *n*-back or working memory task in depressed patients, two have confirmed left DLPFC hyperactivation versus normal controls.[23-25]

Earlier neuroimaging studies had shown similarly aberrant DLPFC activation in depression.[26,27] Thus the Stroop task, which measures the effect of interference on performance of a color identification task, revealed a shift in brain activation in depressed patients to the left DLPFC, a region not recruited for this task in healthy subjects, associated with blunting of the expected ACC increase.[26]

The aberrant DLPFC and ACC activation associated with normal performance in depressed subjects may reflect several problems: (i) an inefficient task-related neural network reflecting difficulty in organizing neural activity and an abnormal signal-to-noise ratio indicative of dopaminergic dysfunction (Daniel R. Weinberger, National Institutes of Health Neuroscience Center at Saint Elizabeth's, Washington, DC 20032, personal communication); (ii) structural brain abnormalities within the working memory network; (iii) excessive subjective effort (volition) or task engagement; and (iv) difficulty in inhibiting limbic structure activation during a cognitive task, reflecting an inability to allocate resources to the external world.[22]

In healthy subjects, ACC activation may reflect the intentional amount of effort (volition) that a subject uses in a task. The ACC also aids cognition by detecting conflict and monitoring error during

information processing.[28] It may contribute to executive processes via the on-line detection of processing conflicts that impair performance.[29] During the *n*-back task, depressed patients may need to monitor putative errors and conflict more than controls, which could account for the greater ACC activation. This hypothesis finds support from a recent event-related potential study showing that depressed patients have abnormal error-related component activation reflecting excessive error monitoring.[30] The dorsal ACC has strong connections with the DLPFC. ACC activation may signal to the brain the need for controlled processing and the DLPFC could be critical for this form of controlled processing.

In healthy subjects, fMRI studies have shown that increasing cognitive demand engages a pattern of brain activation characterized by a balance between increasing activity in cortical cognitive areas and decreasing activity in limbic and paralimbic structures, eg, ventromedial prefrontal regions.[31] Limbic deactivation may represent a gating function aimed at inhibiting emotional interference during cognitive effort. In our *n*-back study, depressed patients had more difficulties than normal controls in deactivating the medial prefrontal cortex.[22,24] Abnormal corticolimbic interaction may subserve performance decrements in effortful tasks in depression,[22] as suggested by the fMRI evidence, obtained at rest and during activation, of imbalance in corticolimbic activity and connectivity in depression.[32,33]

The mechanisms mediating "corticolimbic failure" in depression are unelucidated, but presumably involve genetic factors as well as developmental insults and environmental stressors.[34-36] In this model of dynamic brain adaptation in depression, foci of network dysfunction identified in the baseline depressed state can be considered both as etiological abnormalities and as sites of adaptive and maladaptive compensatory processes.

Brain changes with antidepressant treatment

Treatments for depression can be similarly viewed within this corticolimbic framework. Functional neuroimaging can help to identify the pathways mediating the changes in depression and treatment response. Most such studies have assessed depressed patients using PET or fMRI before and after treatment for 6, 8, or 10 weeks, systematically assessing the regional brain changes associated with clinical response, and evaluating treatment-specific effects and differences between responders and nonresponders.

Study drugs have included SSRIs (eg, fluoxetine,[37] paroxetine,[38-40] and sertraline),[41] tricyclics (eg, imipramine),[42] the serotonin norepinephrine reuptake inhibitor venlafaxine,[43-46] and the atypical antidepressant bupropion, a norepinephrine and dopamine reuptake inhibitor.[47] Changes have been reported in several areas of the cortex (dorsolateral, medial, and ventral prefrontal regions, and parietal region), limbic system (cingulate, amygdala, insula), and subcortex (caudate, thalamus). Almost all studies have reported the normalization of many pretreatment regional abnormalities, with brain metabolism and blood flow ceasing to differ between patients and controls. Improvement of frontal hypometabolism is the best replicated finding.[48,49] However, correction of frontal hypermetabolism has also been described with venlafaxine and paroxetine.[39,50] Posttreatment changes in metabolic activity also occur in brain regions that did not differ from controls at baseline.[41,51] Clinical heterogeneity, compensatory processes, and treatment-specific effects may account for these divergent findings.

Studies comparing responders and nonresponders to a given treatment have identified the brain changes specific to clinical response. In a study of the time course of regional metabolic changes with fluoxetine in unipolar depression, patients were divided into responders (reduction >50% in the Hamilton depression rating scale) and nonresponders after 6 weeks of treatment.[37] At 1 week, both groups had similar brain changes (brain stem and hippocampal increases; posterior cingulate decrease) and no clinical changes. At 6 weeks, clinical responders, but not nonresponders, developed specific limbic and striatal decreases (subgenual cingulate, hippocampus, insula, and pallidum), and brain stem and dorsal cortical increases (prefrontal, parietal, anterior, and posterior cingulate). These findings were confirmed with venlafaxine and bupropion.[14,47] The fact that depressed patients who respond to placebo[52] show the same brain changes as those who respond to cognitive-behavioral therapy[50] suggests a final common pathway for the clinical remission of depression achieved through both pharmacologic and non-pharmacologic treatments. However, the presence of specific brainstem and hippocampal changes in fluoxetine-treated patients supports the hypothesis that both treatment-specific and response-specific effects can be identified.[53]

In light of these differences between responders and nonresponders, an obvious related question is whether baseline regional activities predict treatment outcome. Several studies have found that pretreatment metabolic activity in the rostral (pregenual) cingulate uniquely distinguishes medication responders from nonresponders.[40,54,55] In an fMRI study, amygdalar reactivity to emotional faces in depressed patients predicted symptom reduction after antidepressant treatment for 8 months.[56] The amygdala has long been implicated in antidepressant drug action via serotoninergic pathway inhibition. Never-depressed volunteers receiving citalopram 20 mg/day for 1 week showed decreased amygdalar responses to masked presentation of threat stimuli compared to volunteers receiving placebo, suggesting that SSRIs modulate amygdalar responses directly without elevating mood in normal subjects.[57] Other studies by the same Oxford group have shown that single or repeated dosing with reboxetine may enhance speed of categorization and recognition of positive emotional words in normal controls. This positive bias induced by an antidepressant without concomitant mood change points to a cognitive effect via the modulation of limbic network reactivity (medial prefrontal cortex, amyg-

dala).[58,59] This interpretation is consistent with the well-known anxiolytic properties of SSRIs and the emotional bias observed in depressed patients.

Summary and future direction

Abnormal corticolimbic balance and connectivity may subserve cognitive deficits and emotional bias in acute depression. Reciprocal corticolimbic interaction (cortical increases / limbic decreases) is critical for clinical remission, whatever the treatment used. By improving connectivity in dysfunctional corticolimbic pathways, antidepressants may help the brain to restore cognitive and emotional homeostasis. Increased pretreatment activity in the rostral anterior cingulate and amygdala may predict clinical response to pharmacotherapy. The studies we have discussed have described the short-term effects of antidepressants in acute depression. Cognitive and emotional studies are needed in remitters and subjects at high risk to elucidate the neural correlates of vulnerability to depression. Preliminary studies with mood induction have emphasized the role of the medial prefrontal cortex in this regard.[60] However, long-term imaging studies are needed to define the neural correlates of sustained remission. Preliminary data and recent findings with deep brain stimulation suggest that maintaining persistent control of activity in the subgenual cingulate cortex (Brodman area 25) may prevent relapse of depression.[61] Perhaps the most fundamental requirement is for further clinical and experimental in vivo and in vitro studies to identify the genetic and environmental determinants of structural and functional plasticity within the neural network regulating mood and affective behavior, and thus to prepare the ground for the development of novel antidepressant treatments. ❐

REFERENCES

1. Drevets WC. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Prog Brain Res*. 2000;126:413-431.
2. Mayberg HS, Fossati P. Dysfunctional limbic-cortical circuits in major depression: a functional neuroimaging perspective. In: Barch DM, ed. *Cognitive and Affective Neuroscience of Psychopathology*. Oxford, UK: Oxford University Press; In press.
3. Ketter TA, George MS, Kimbrell TA, et al. Functional brain imaging, limbic function, and affective disorders. *Neuroscientist*. 1996;2:55-65.
4. Bench CJ, Friston KJ, Brown RG, et al. Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. *Psychol Med*. 1993;23:579-590.
5. Stuss DT, Benson DF. Neuropsychological studies of the frontal lobes. *Psychol Bull*. 1984;95:3-28.
6. Fossati P, Ergis AM, Allilaire JF. [Executive functioning in unipolar depression: a review]. *Encéphale*. 2002;28:97-107.
7. Osuch EA, Ketter TA, Kimbrell TA, et al. Regional cerebral metabolism associated with anxiety symptoms in affective disorder patients. *Biol Psychiatry*. 2000;48:1020-1030.
8. Dolan RJ, Bench CJ, Brown RG, et al. Neuropsychological dysfunction in depression: the relationship to regional cerebral blood flow. *Psychol Med*. 1994; 24:849-857.
9. Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. The neural basis of mood-congruent processing biases in depression. *Arch Gen Psychiatry*. 2002;59:597-604.
10. Brody AL, Saxena S, Mandelkern MA, et al. Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biol Psychiatry*. 2001;50:171-178.
11. Leppänen JM. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Curr Opin Psychiatry*. 2006;19:34-39.
12. Gotlib IH, Krasnoperova E, Neubauer D, Joorman J. Attentional biases for negative interpersonal stimuli in clinical depression. *J Abnorm Psychol*. 2004; 113:127-135.
13. Leppänen JM, Milders M, Bell JS, et al. Depression biases the recognition of neutral faces. *Psychiatry Res*. 2004;128:123-133.
14. Fu CH, Williams SC, Cleare AJ, et al. Attenuation of the neural responses to sad faces in major depression by antidepressant treatment. *Arch Gen Psychiatry*. 2004;61:877-889.
15. Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry*. 2002;51:693-707.
16. Canli T, Sivers H, Thomason ME, Whitfield-Gabrieli S, Gabrieli JD, Gotlib IH. Brain activation to emotional words in depressed vs healthy subjects. *Neuroreport*. 2004;15:2585-2588.
17. Epstein J, Pari H, Kocsis JH, et al. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *Am J Psychiatry*. 2006;163:1784-1790.
18. Hasher L, Zacks RT. Automatic and effortful processes in memory. *J Exp Psychol Gen*. 1979;108:356-389.
19. Hartlage S, Alloy LB, Vazquez C, Dykman B. Automatic and effortful processing in depression. *Psychol Bull*. 1993;113:247-278.
20. Jouvent R, Dubal S, Fossati P. The cost of pleasure. In: Sebanz N, Prinz W, eds. *Disorders of Volition*. Cambridge, Mass: MIT Press; 2006:307-325.
21. Dubal S, Jouvent R. Time-on-task effect in trait anhedonia. *Eur Psychiatry*. 2004;19:285-291.
22. Harvey PO, Fossati P, Pochon JB, et al. Brain Resources and cognitive effort in depression: a fMRI study using the *n*-back task. *Neuroimage*. 2005;26:860-869.
23. Matsuo K, Glahn DC, Peluso MA, Hatch JP. Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder. *Mol Psychiatry*. 2007;12:158-166.
24. Rose EJ, Simonotto E, Ebmeier KP. Limbic overactivity in depression during preserved performance on the n-back task. *Neuroimage*. 2006;29:203-215.
25. Walter H, Wolf RC, Spitzer M, Vasic N. Increased left prefrontal activation in patients with unipolar depression: an event-related, parametric, performance-controlled fMRI study. *J Affect Disord*. In press.
26. George MS, Ketter TA, Post RM. Prefrontal cortex dysfunction in clinical depression. *Depression*. 1994; 2:59-72.
27. Videbech P, Ravnkilde B, Kristensen S, et al. The Danish PET/depression project: poor verbal fluency performance despite normal prefrontal activation in patients with major depression. *Psychiatry Res*. 2003; 123:49-63.
28. Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. *Science*. 2004;306:443-447.
29. Carter CS, Botvinick MM, Cohen JD. The contribution of the anterior cingulate cortex to executive processes in cognition. *Rev Neurosci*. 1999;10:49-57.
30. Chiu PH, Deldin PJ. Neural evidence for enhanced error detection in major depressive disorder. *Am J Psychiatry*. 2007;164:608-616.
31. Pochon JB, Levy R, Fossati P, et al. The neural system that bridges reward and cognition in humans: an fMRI study. *PNAS*. 2002;99:5669-5674.
32. Anand A, Li Y, Wang Y, et al. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biol Psychiatry*. 2005;57:1079-1088.
33. Greicius MD, Flores BH, Menon V, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cortex and thalamus. *Biol Psychiatry*. In press.
34. Frank E, Thase ME. Natural history and preventive treatment of recurrent mood disorders. *Ann Rev Med*. 1999;50:453-468.
35. Jacobs BL, Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. *Mol Psychiatry*. 2000;5:262-269.
36. Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *Am J Psychiatry*. 2001;158:582-586.
37. Mayberg HS, Brannan SK, Mahurin RK, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol Psychiatry*. 2000;48:830-843.
38. Smith GS, Reynolds CF, Pollock B, et al. Cerebral glucose metabolic response to combined total sleep deprivation and antidepressant treatment in geriatric depression. *Am J Psychiatry*. 1999;156:683-689.
39. Brody AL, Saxena S, Stoessel P, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy. *Arch Gen Psychiatry*. 2001;58:631-640.
40. Kennedy SH, Evans K, Kruger S, et al. Changes in regional glucose metabolism with PET following paroxetine treatment for major depression. *Am J Psychiatry*. 2001;158:899-905.
41. Buchsbaum MS, Wu J, Siegel BV, et al. Effect of sertraline on regional metabolic rate in patients with affective disorder. *Biol Psychiatry*. 1997;41:15-22.
42. Hurwitz TA, Clark C, Murphy E, Klonoff H, Martin WR, Pate BD. Regional cerebral glucose metabolism in major depressive disorder. *Can J Psychiatry*. 1990; 35:684-688.
43. Martin SD, Martin E, Rai SS, et al. Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride. *Arch Gen Psychiatry*. 2001;58:641-664.
44. Davidson RJ, Irwin W, Anderle MJ, Kalin NH. The neural substrates of affective processing in depressed patients treated with venlafaxine. *Am J Psychiatry*. 2003;160:64-75.
45. Davies J, Lloyd KR, Jones IK, Barnes A, Pilowsky LS. Changes in regional cerebral blood flow with venlafaxine in the treatment of major depression. *Am J Psychiatry*. 2003;160:374-376.
46. Schaefer HS, Putnam KM, Benca RM, Davidson RJ. Event-related functional magnetic resonance imaging measures of neural activity to positive social stimuli in pre- and post-treatment depression. *Biol Psychiatry*. In press.
47. Little JT, Ketter TA, Kimbrell TA, et al. Bupropion and venlafaxine responders differ in pretreatment regional cerebral metabolism in unipolar depression. *Biol Psychiatry*. 2005;57:220-228.
48. Baxter LR Jr, Schwartz JM, Phelps ME, et al. Re-

duction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry*. 1989;46:243-250.
49. Martinot JL, Hardy P, Feline A, et al. Left prefrontal glucose hypometabolism in the depressed state: a confirmation. *Am J Psychiatry*. 1990;147:1313-1317.
50. Goldapple K, Segal Z, Garson C, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. *Arch Gen Psychiatry*. 2004;61:34-41.
51. Bench CJ, Frackowiak RS, Dolan RJ. Changes in regional cerebral blood flow on recovery from depression. *Psychol Med*. 1995;25:247-251.
52. Mayberg HS, Silva JA, Brannan SK, et al. The functional neuroanatomy of the placebo effect. *Am J Psychiatry*. 2002;159:728-737.
53. Mayberg HS. Modulating limbic-cortical circuits in depression: targets of antidepressant treatments. *Semin Clin Neuropsychiatry*. 2002;7:255-268.
54. Mayberg H, Brannan S, Mahurin R, et al. Cingulate function in depression: A potential predictor of treatment response. *Neuroreport*. 1997;8:1057-1061.
55. Pizzagalli D, Pascual-Marqui RD, Nitschke JB. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *Am J Psychiatry*. 2001;158:405-415.
56. Canli T, Cooney RE, Goldin P, et al. Amygdala reactivity to emotional faces predicts improvement in major depression. *Neuroreport*. 2005;16:1267-1270.
57. Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biol Psychiatry*. 2006;59:816-820.
58. Miskowiak K, Papadatou-Pastou M, Cowen PJ, Goodwin GM, Norbury R, Harmer CJ. Single dose antidepressant administration modulates the neural processing of self-referent personality trait words. *Biol Psychiatry*. In press.
59. Norbury R, Mackay CB, Cowen PJ, Goodwin GM, Harmer CJ. The effects of reboxetine on emotional processing in healthy volunteers: an fMRI study. *Neuroimage*. In press.
60. Keightley ML, Seminowicz DA, Bagby RM, Costa PT, Fossati P, Mayberg HS. Personality influences limbic-cortical interactions during sad mood induction. *Neuroimage*. 2003;20:2031-2039.
61. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005;45:651-660.

APPORTS DE L'IMAGERIE CÉRÉBRALE FONCTIONNELLE À LA PHYSIOPATHOLOGIE DE LA DÉPRESSION

Les études d'imagerie cérébrale fonctionnelle suggèrent que la dépression est une maladie impliquant de multiples systèmes constitués par des structures corticolimbiques discrètes mais fonctionnellement liées. On peut ainsi observer des anomalies touchant le cingulum antérieur, le cortex préfrontal latéral et médian, l'amygdale et l'hippocampe. Celles-ci sont à l'origine des interactions corticolimbiques anormales qui sous-tendent les déficits cognitifs et les biais émotionnels caractéristiques de la dépression. Dans cette maladie, il existe en effet un biais cognitif privilégiant le traitement des informations émotionnelles négatives en résonance avec l'humeur altérée et les soucis du patient. Ceci traduit probablement une prolongation du traitement involontaire des stimuli émotionnels et l'altération de la modulation des réponses émotionnelles aux stimuli négatifs. Le traitement antidépresseur, médicamenteux ou psychothérapeutique, contribuerait à restaurer l'homéostasie cérébrale cognitive et émotionnelle en améliorant la connectivité des voies corticolimbiques défaillantes. Une augmentation de l'activité dans le cingulum rostral antérieur et l'amygdale avant traitement est prédictive de la réponse clinique aux traitements antidépresseurs. Les études d'imagerie cérébrale, en associant les explorations structurales et fonctionnelles, pourraient contribuer à l'avènement de nouveaux traitements antidépresseurs régulateurs de la plasticité structurale et fonctionnelle au sein du réseau nerveux qui commande les comportements affectifs et de l'humeur.

PSYCHOEDUCATIONAL INTERVENTIONS TARGETING THE CORE SYMPTOMS OF DEPRESSION

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Depressive disorders have a high prevalence[1,2] and incidence,[3] and are associated with huge losses in quality of life for patients and their relatives,[4] high mortality rates,[5,6] high service consumption, and enormous economic costs.[7,8] They currently account for the world's fourth largest disease burden, and are on track to become the largest disease burden in high-income countries by 2030.[9]

Most depressive disorders respond satisfactorily to drug therapy and/or psychological intervention. Dozens of well-designed randomized controlled trials bear out the efficacy of pharmacological treatments,[10] while other evidence indicates that electroconvulsive therapy,[11,12] bright light therapy,[13] and exercise[14] may also be effective. Further randomized trials testify to the efficacy of a broad spectrum of psychological interventions, including cognitive behavioral therapy (CBT),[15,16] behavioral activation treatments,[17] marital therapy,[18] problem-solving therapy,[19] and interpersonal psychotherapy.[16] These interventions are effective not only in adults with depression, but also in the elderly,[20] in postpartum depression,[21] and depression associated with general medical disorders, including multiple sclerosis,[22] stroke,[23] and cancer.[24]

Psychoeducational approaches are an increasingly important variant of psychological intervention. Most are CBT-based. Not only is CBT the state of the art approach to depression, as shown in dozens of well-designed trials, but its techniques tend to be very straightforward, targeted at current problems and situations, and thus readily decomposable into relatively easy steps, unlike most common psychological interventions, such as psychodynamic or interpersonal therapies. Interventions focus on the core symptoms of unipolar depression, namely, depressed mood and anhedonia. The CBT techniques used to act on these core symptoms include cognitive restructuring and activity scheduling.

SELECTED ABBREVIATIONS AND ACRONYMS

BDI	Beck Depression Inventory
CBT	cognitive behavioral therapy
CWD	Coping With Depression (course)

Psychoeducational intervention on the core symptoms of depression: the Coping With Depression course

By far the best studied psychoeducational treatment for depression, widely used in the US, UK, Netherlands, Germany, Finland, and Norway, is the Coping With Depression course (CWD), originally

Depressive disorders have a high prevalence and incidence, and are associated with a huge burden of disease and economic costs. Most respond satisfactorily to drug therapy and/or psychological intervention, in particular to psychoeducation. By far the best-studied example of this approach is the Coping With Depression course (CWD). Widely used in several countries, the CWD comprises 8 to 16 sessions, targets the core symptoms of depressed mood and anhedonia, and can be delivered in individual, group, or guided self-help formats. It is a highly structured cognitive-behavioral intervention based on social learning theory. The therapist is essentially an instructor and participants are students rather than patients; there is no traditional psychotherapeutic relationship between the two. The CWD is highly flexible and can be adapted to a variety of contents, target populations, and goals, including the treatment of established disease, and primary and secondary prevention. Randomized studies have shown that it lowers the incidence of depressive disorders in subthreshold depression, relieves existing depressive disorders, and may also reduce the relapse rate. It is also more effective in mild-to-moderate depression, in subjects with higher expectations of its results, those receiving more social support, and those who feel in control of their lives. Delivery over the Internet has many advantages and is becoming increasingly common.

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Keywords: *cognitive behavioral therapy; core symptom; depression; Internet; psychoeducation*

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developed by Peter Lewinsohn at the Oregon Research Institute in Eugene, Oregon.[25] Its theoretical basis is social learning theory, which views depression as associated with a decrease in pleasant and an increase in unpleasant person-environment interactions. It sees the problems presented by depressed individuals as cognitive and behavioral patterns which can be unlearned or relearned. CWD content is thus cognitive-behavioral, and designed to train skills that can be used by the depressed individual to change these cognitive and behavioral patterns. The modules focus on cognitive skills, relaxation, social skills, and how to increase the number of pleasant events *(Table I)*.

The cognitive skills are based on Aaron Beck's cognitive therapy[26] and Albert Ellis' rational emotive behavior therapy.[27] Lewinsohn developed the pleasant-events approach.[28] Each part of the skills training follows the same basic format. An important characteristic is that therapists are more like instructors and patients more like students. First, for 1-2 weeks, the patient-students collect information on the subject matter (negative thoughts, pleasant/unpleasant events, stressful events, social events). They then set a goal for what they want to change, and develop a systematic plan to achieve that goal. Lastly, they start working with the plan, improving it, and determining whether it alleviates the depression.

The original CWD comprised 12 sessions, plus two boosters 1 and 6 months after completing the course. Homework is a basic component. Patients record their cognitions and behaviors, and work on their self-change plans at home. The CWD regularly stresses that the most important changes are those that take place in everyday life.

The psychoeducational CWD is highly structured. The patient-student works more or less independently through a standardized psychological treatment protocol that is book or Web-based. Although treatments are mainly delivered in a group format, individual[29] and guided self-help formats[29-31] are also available, with Internet delivery coming increasingly to the fore. Since there is no traditional psychotherapeutic relationship between the professional delivering the intervention and the patient-student, treatment-instruction can be delivered by a variety of health care professionals, including psychologists, general practitioners, social workers, and nurses. Experience has shown, however, that intensive training is required to do so successfully.

Therapist-instructors may differ significantly from one other in enthusiasm, clarity, warmth, and group cohesiveness, as rated by their patient-students, but there is no significant relationship between a range of instructor characteristics and course effectiveness.[32,33] This indicates that the CWD is a psychological treatment for depression that can be used outside the psychologist's office, eg, in the classroom.

A further characteristic setting the CWD apart from other CBT interventions is the toolbox idea: patient-students learn all the skills that help them cope with their depression and that more or less fit the theoretical model. These skills address several specific target behaviors, as well as more general components (self-monitoring, contracting, progressive goal attainment) that are considered critical for successful CBT.

Content	Cognitive behavioral therapy for depression in a psychoeducational format
Target population	Patients with mild-to-moderate depression. Those with severe depression may also participate, but should be offered additional therapy
Number of sessions	8 to 16 (depending on goals and target population)
Exclusion criteria	Minimal, to comply with the psychoeducational approach: – Other severe mental disorder (bipolar disorder, suicidal behavior, addiction, psychosis) – Severe hearing difficulties or visual handicap *NB: Medication and other psychotherapy are NOT exclusion criteria*
Skills taught	– **Activity scheduling** is a behavioral treatment teaching patients how to monitor their mood and daily activities, and how to increase the number of pleasant activities and positive interactions with their environment – **Cognitive restructuring** views depression as caused by dysfunctional cognitions. Patients learn to identify their dysfunctional cognitions related to depression. They record the situations in which the cognitions arise and work out how they can challenge and change them so that they no longer trigger depression – **Social skills training** teaches skills that patients can use when dealing with others, including assertiveness training, communication skills, and conflict management – **Relaxation techniques** have no proven effect on depression, but are much appreciated by patients. Applied relaxation is the most widely used technique. Patients learn to relax before entering stressful situations
Theoretical basis	Social learning theory
Some basics	– Teacher/student rather than therapist/patient relationship – Intervention focuses on the patient's current life and how it can be changed in order to improve mood; early life experiences and the patient's character are never discussed – Homework is very important (1/2 – 1 hour per day)

Table I. Outline of the Coping With Depression course.

◆ ***Flexibility of the Coping With Depression (CWD) course***

The CWD is highly flexible. Although originally designed for use with adults aged between 20 and 55, it is readily adaptable to the needs of specific target populations and to different areas of mental health care, in each case with appropriate modifications. Thus, it has been examined in different age groups, including adolescents[34-36] (with the addition of conflict-solving skills and a less formal presentation), and the elderly[37-39] (for whom the materials have been simplified). Variants have been developed for minority groups,[40,41] caregivers of the elderly,[42] people with chronic medical illness[43] (for whom "mood improvement" has replaced "depression" in all materials), women with postpartum depression,[44] and menopausal women.[45] The CWD has also been used to help smokers with a history of depression to stop smoking.[46] Treatment goals vary from the prevention of new disease in subjects already showing

First author, year	Target population	Recruitment	Inclusion criteria	Treatment	N	Treatment schedule	Follow-up	DO (%)	Effect on incidence of MDD/dysthymia
Allart, 2003[47]	Adults (18-65 y)	Via local media	BDI ≥10 no MDD	1. CBT 2. TAU	61 41	12 × 2 h CBT group sessions	6 mo 1 y, 2 y	25.0	At 2 years: no significant effect
Clarke, 2001[48]	Adolescents (13-18 y)	Via health maintenance organization	CESD >24 or ≥1 *DSM IV* criteria & parent treated for MDD in past year, no MDD	1. CBT 2. TAU	43 47	15 × 1 h CBT group sessions	1 y, 2 y	Not reported	At 1 year: 14.5% in treatment group vs 25.7% in controls (P<0.05)
Clarke, 1995[49]	Adolescents (15 -16 y)	School screening	CESD ≥24 no MDD	1. CBT 2. TAU	55 70	15 × 3/4 h CBT group sessions	6 mo 1 y	17.3	At 1 year: 9.3% in treatment group vs vs 28.8% in controls (P<0.01)
Willemse, 2004[31]	Adults (18-65 y)	Primary care screening	1 core symptom of *DSM IV* MDD + 1-3 other symptoms but no MDD	1. CBT 2. TAU	107 109	Guided self-help CBT (self-help book + 6 brief telephone contacts)	1 y	37.0	At 1 year: 12% in treatment group vs 18% in controls (P<0.05)

Table II. Efficacy of the Coping With Depression course on the incidence of major depressive disorder in subjects with subthreshold depression.
Abbreviations: BDI, Beck Depression Inventory; CBT, cognitive behavioral therapy; CESD, Center for Epidemiologic Studies Depression Scale; DO, dropout rate; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed;* MDD, major depressive disorder; TAU, treatment as usual.

some symptoms of major depression, but not yet meeting full-blown criteria, through the regular treatment of depressed patients, to the prevention of relapse following successful treatment.

◆ *Efficacy of the Coping With Depression course*

Four studies have evaluated the prophylactic efficacy of the CWD in subjects with subthreshold depression, ie, with clinically relevant depressive symptoms not yet meeting the criteria for major depression or dysthymia *(Table II)*.[31,47-49] Three concluded that the CWD had a significant effect on the incidence of major depression. However, it remains unclear whether intervention prevented the onset of major depression altogether or simply postponed it.

Several studies have assessed the therapeutic efficacy of the CWD in established depression. In a meta-analysis of seven randomized controlled trials, we calculated the mean standardized effect size as 0.62 (95% confidence interval: 0.44-0.85).[50] This is similar to that for other psychological[16] and pharmacological treatments.[10] Several subsequent studies, including in elderly,[38,39] postpartum depression,[44] minority groups,[41] and depressed patients in the general population,[51] have reached similar conclusions, namely that the CWD is an effective treatment of depressive disorders.

Several efficacy questions remain unanswered. No study has compared the CWD to pharmacological or other common psychological treatments, such as standard cognitive therapy or interpersonal therapy. Furthermore, most studies in the meta-analysis used waiting list control groups. In a recent randomized trial comparing the CWD to problem-solving treatment and a no-treatment control group, the CWD was effective in the short term, but less so than problem-solving therapy.[51]

Longer-term efficacy is less clear. The meta-analysis found the mean level of depressive symptoms unchanged at 6 months' follow-up.[50] However, this result was based on only six studies and no control groups were available at 6 months because most studies used a waiting list control group. One study examined outcome at 1 and 3 years' follow-up[52]: the relapse rate 60 weeks after completing the CWD was 54%. It was higher in subjects with a history of previous major depressive episode, those in poor health, those unsatisfied in important life areas, younger subjects, and those more seriously depressed at the outset. The relapse rate was similar to that in other psychological and pharmacological treatments of depression. However, another study conducted after successful inpatient treatment for major depressive episode reported 14% relapse at 6 months in patients receiving CWD after recovery versus 43% in controls.[53] Thus, experience with the CWD suggests that CBT can be conducted in a psychoeducational format while retaining both short-term and long-term efficacy.

Multiple regression analyses using the post-test Beck Depression Inventory (BDI) score as the dependent variable and a series of other variables as predictors have identified three significant effect predictors of the CWD in adults[54,55]:

- Those with higher expectations of the course.
- Those receiving more social support.
- Those who feel in control of their lives.

Conversely, subjects with high pretest BDI scores (severe disease) have high post-test scores. The following were unrelated to outcome: intelligence, proportion of homework performed, introversion, irrational thoughts, suicidality, alcohol or drug abuse, and acceptance of the theoretical model of the CWD. In adolescents, post-CWD improvement is greater in those with more depressive symptoms and lower in those with a depressive family history; efficacy is also lower if the adolescents feel less cohesion in their CWD group.[36,56]

◆ *Coping With Depression course: advantages, disadvantages and future prospects*

The CWD is an effective and flexible intervention that can be used in subthreshold depression to prevent the onset of major depression, but also as a

treatment for major depression, and for relapse prevention. However, in addition to the absence of comparative efficacy studies and the issue of long-term efficacy, several questions remain unanswered. We do not know whether the CWD improves depressed patients' ability to concentrate at work. Nor has its effects on relatives been seriously examined, although clinical experience shows that most relatives are happy that patients are encouraged to focus on positive actions and are stimulated to change their daily lives. However, a parallel intervention targeting parents failed to improve CWD outcome in depressed adolescents.[35]

The most recent positive development in psychoeducational interventions for depression is Internet delivery. It has many advantages: it saves therapist time, abolishes the need to schedule therapist appointments, reduces the stigma of going to a therapist, saves traveling time, lowers care costs, shortens waiting lists, allows patients to work at their own pace, and can be programmed to enhance motivation by presenting a wide range of attractive audiovisual information with instructions given in voices selected for their gender, age, language, and accent; it can also be packaged in the client's preferred game format, and can quickly and automatically report progress and self-ratings.[57] On the other hand, patients may be unable to complete a self-help intervention, which may result in a negative experience that could worsen a depressive episode. Nor does everyone have ready access to the Internet. It is not acceptable for all patients, and may miss subtle nonverbal and verbal clues to client misunderstandings.[57] However, a 2007 meta-analysis of randomized controlled trials of Internet-guided self-help programs for mood and anxiety disorders found these interventions to be highly effective when backed by personal support (standardized effect size: 1.00).[58] The Internet thus appears set to increase the utility of the CWD as a psychoeducational intervention in depression, whether for treatment or primary and secondary prevention. ❐

REFERENCES

1. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51:8-19.

2. Bijl R, Ravelli A, Van Zessen G. Prevalence of psychiatric disorder in the general Dutch population. *Soc Psychiatry Psychiatr Epidemiol*. 1998;33:587-595.

3. Bijl RV, Ravelli A. Psychiatric morbidity, service use, and need for care in the general population: Results of the Netherlands Mental Health Survey and Incidence Study. *Am J Public Health*. 2000;90:602-607.

4. De Graaf R, Bijl RV, Ravelli A, Smit F, Vollebergh WA. Predictors of first incidence of DSM-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study. *Acta Psychiatr Scand*. 2002;106:303-313.

5. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. *J Affect Disord*. 2002;72:227-236.

6. Cuijpers P, Schoevers RA. Increased mortality in depressive disorders: A review. *Curr Psychiatry Rep*. 2004;6:430-437.

7. Smit F, Cuijpers P, Oostenbrink J, Batelaan N, de Graaf R, Beekman A. Excess costs of common mental disorders: population-based cohort study. *J Ment Health Policy Econ*. 2006;9:193-200.

8. Cuijpers P, Smit F, Oostenbrink J, de Graaf R, ten Have M, Beekman A. Economic costs of minor depression: A population-based study. *Acta Psychiatr Scand*. 2007;115:229-236.

9. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3:e442 doi:10.1371/journal.pmed.0030442.

10. Anderson IM. Meta-analytic studies on new antidepressants. *Br Med Bull*. 2001;57:161-178.

11. Pagnin D, de Queiroz V, Pini S, Cassano GB. Efficacy of ECT in depression: a meta-analytic review. *J ECT*. 2004;20:13-20.

12. Kho KH, van Vreeswijk MF, Simpson S, Zwinderman AH. A meta-analysis of electroconvulsive therapy efficacy in depression. *J ECT*. 2003;19:139-147.

13. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry*. 2005;162:656-662.

14. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *BMJ*. 2001;322:763-767.

15. Gloaguen V, Cottraux J, Cucherat M, Blackburn IM. A meta-analysis of the effects of cognitive therapy in depressed patients. *J Affect Disord*. 1998;49:59-72.

16. Churchill R, Hunot V, Corney R, et al. A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression. *Health Technol Assess*. 2001;5(35).

17. Cuijpers P, van Straten A, Warmerdam L. Behavioral treatment of depression: A meta-analysis of activity scheduling. *Clin Psychol Rev*. 2007;27:318-326.

18. Barbato A, D'Avanzo B. Marital therapy for depression. *Cochrane Database of Systematic Reviews*. 2006, Issue 2. Art. No.: CD004188.pub2. DOI: 10.1002/14651858.CD004188.pub2.

19. Cuijpers P, van Straten A, Warmerdam L. Problem solving therapies for depression: A meta-analysis. *Eur Psychiatry*. 2007;22:9-15.

20. Cuijpers P, van Straten A, Smit F. Psychological treatment of late-life depression: A meta-analysis of randomized controlled trials. *Int J Geriatr Psychiatry*. 2006;21:1139-1149.

21. Lumley J, Austin MP, Mitchell C. Intervening to reduce depression after birth: A systematic review of the randomized trials. *Int J Technol Assess Health Care*. 2004;20:128-144.

22. Mohr DC, Goodkin DE. Treatment of depression in multiple sclerosis: Review and meta-analysis. *Clin Psychol Sci Pract*. 1999;6:1-9.

23. Hackett ML, Anderson CS, House AO. Interventions for treating depression after stroke. *Cochrane Database of Systematic Reviews*. 2004, Issue 2. Art. No.: CD003437.pub2. DOI: 10.1002/14651858.CD003437.pub2.

24. Sheard T, McGuire P. The effect of psychological interventions on anxiety and depression in cancer patients: results of two meta-analyses. *Br J Cancer*. 1999;80:1770-1780.

25. Lewinsohn PM, Antonuccio DO, Steinmetz-Breckenridge JL, Teri L. *The Coping with Depression Course: A Psychoeducational Intervention for Unipolar Depression*. Eugene, Ore: Castalia Publishing Company; 1984.

26. Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive Therapy of Depression*. New York, NY: Guilford Press; 1979.

27. Ellis A, MacLaren C. *Rational Emotive Behavior Therapy: A Therapist's Guide*. 2nd ed. Atascadero, Calif: Impact Publishers; 2005.

28. Lewinsohn PM. The behavioral study and treatment of depression. In: Calhoun S, Adams HE, Mitchell KM, eds. *Innovative Treatment Methods in Psychopathology*. New York, NY: Wiley; 1975.

29. Brown RA, Lewinsohn PM. A psychoeducational approach to the treatment of depression: comparison of group, individual and minimal contact procedures. *J Consult Clin Psychol*. 1984;52:774-783.

30. Scogin F, Hamblin D, Beutler L. Bibliotherapy for depressed older adults: A self-help alternative. *Gerontologist*. 1987;27:383-387.

31. Willemse GR, Smit F, Cuijpers P, Tiemens BG. Minimal contact psychotherapy for sub-threshold depression in primary care: a randomised trial. *Br J Psychiatry*. 2004;185:416-421.

32. Antonuccio DO, Lewinsohn PM, Steinmetz JL. Identification of therapist differences in group treatment for depression. *J Consult Clin Psychol*. 1982;50:435-443.

33. Antonuccio DO, Davis C, Lewinsohn PM, Breckenridge JS. Therapist variables related to cohesiveness in a group treatment for depression. *Small Group Behav*. 1987;18:557-564.

34. Clarke GN, Lewinsohn PM. The Coping with Depression course: A group psychoeducational intervention for unipolar depression. *Behav Change*. 1989;6:54-69.

35. Lewinsohn PM, Clarke GN, Hops H, Andrews J. Cognitive-behavioral treatment for depressed adolescents. *Behav Ther*. 1990;21:385-401.

36. Lewinsohn PM, Clarke GN, Rohde P, Hops H, Seeley JR. A course in coping: a cognitive-behavioral approach to the treatment of adolescent depression. In: Hibbs ED, Jensen PS, eds. *Psychosocial Treatments for Child and Adolescent Disorders: Empirically based Strategies for Clinical Practice*. Washington, DC: American Psychological Association; 1996, pp. 109-136.

37. Breckenridge JS, Zeiss AM, Thompson LW. The Life Satisfaction course: An intervention for the elderly. In: Munoz RF, ed. *The Prevention of Depression: Research Directions*. New York, NY: Hemisphere Publications; 1986.

38. Hautzinger M, Welz S. [Cognitive behavioral therapy for depressed older outpatients—A controlled, randomized trial]. *Z Gerontol Geriat*. 2004;37:427-435.

39. Haringsma R, Engels GI, Cuijpers P, Spinhoven P. Effectiveness of the Coping With Depression (CWD) course for older adults provided by the community-based mental health care system in the Netherlands: a randomized controlled field trial. *Int Psychogeriatr*. 2006;18:307-325.

40. Organista KC, Muñoz RF, Gonzalez G. Cognitive-behavioral therapy for depression in low-income and minority medical outpatients: description of a program and exploratory analyses. *Cogn Ther Res*. 1994;18:241-259.

41. Miranda J, Chung JY, Green BL, et al. Treating depression in predominantly low-income young minority women. *JAMA*. 2003;290:57-63.

42. Lovett S, Gallagher D. Psychoeducational interventions for family caregivers: Preliminary efficacy

data. *Behav Ther.* 1988;19:321-330.
43. Cuijpers P. Prevention of depression in chronic general medical disorders; a pilot study. *Psychol Rep.* 1998;82:735-738.
44. Milgrom J, Negri LM, Gemmill AW, McNeil M, Martin PR. A randomized controlled trial of psychological interventions for postnatal depression. *Br J Clin Psychol.* 2005;44:529-542.
45. Ayen I, Hautzinger M. [Cognitive behavioral therapy in menopausal depression: a controlled randomized interventional study]. *Z Klin Psychol Psychother.* 2004;33:290-299.
46. Muñoz RF, Van Oss MB, Posner SF, Pérez-Stable EJ. Mood management mail intervention increases abstinence rates for Spanish-speaking Latino smokers. *Am J Community Psychol.* 1997;25:325-343.
47. Allart E, Hosman CM, Hoogduin CA, Schaap CP. The "Coping with Depression" Course: short term outcomes and mediating effects of a randomized controlled trial in the treatment of subclinical depression. *Behav Ther.* 2003;34:381-396.
48. Clarke GN, Hornbrook M, Lynch F, et al. A randomized trial of a group cognitive intervention for preventing depression in adolescent offspring of depressed parents. *Arch Gen Psychiatry.* 2001;58:1127-1134.
49. Clarke GN, Hawkins W, Murphy M, Sheeber LB. Targeted prevention of unipolar depressive disorder in an at-risk sample of high school adolescents: a randomized trial of group cognitive intervention. *J Am Acad Child Adolesc Psychiatry.* 1995;34:312-321.
50. Cuijpers P. A psycho-educational approach to the treatment of depression; a meta-analysis of Lewinsohn's 'Coping with Depression' course. *Behav Ther.* 1998;29:521-533.
51. Dowrick C, Dunn G, Ayuso-Mateos JL, et al. Problem solving treatment and group psychoeducation for depression: Multicentre randomised controlled trial. *BMJ.* 2000;321:1450-1454.
52. Gonzales LR, Lewinsohn PM, Clarke GN. Longitudinal follow-up of unipolar depressives: an investigation of predictors of relapse. *J Consult Clin Psychol.* 1985;53:461-469.
53. Kühner C, Angermayer MC, Veiel HO. [Efficacy of a cognitive behavioral therapy group program for relapse prevention in depressive disease]. *Verhaltensther.* 1994;4:4-12.
54. Steinmetz JL, Lewinsohn PM, Antonuccio DO. Prediction of outcome in a group intervention for depression. *J Consult Clin Psychol.* 1983;51:331-337.
55. Hoberman HM, Lewinsohn PM, Tilson M. Group treatment of depression: individual predictors of outcome. *J Consult Clin Psychol.* 1988;56:393-398.
56. Clarke G, Hops H, Lewinsohn PM, Andrews J, Seeley JR, Williams J. Cognitive-behavioral group treatment of adolescent depression: prediction of outcome. *Behav Ther.* 1992;23:341-354.
57. Marks IM, Cavanagh K, Gega L. Maudsley Monographs No. 45. *Hands-on Help: Computer-Aided Psychotherapy.* Hove, UK: Psychology Press; 2007.
58. Spek V, Cuijpers P, Nyklíãek I, Riper H, Keyzer J, Pop V. Internet-based cognitive behavior therapy for mood and anxiety disorders: a meta-analysis. *Psychol Med.* 2007;37:319-328.

MESURES PSYCHOÉDUCATIONNELLES CIBLANT LES SYMPTÔMES MAJEURS DE LA DÉPRESSION

*La prévalence et l'incidence des troubles dépressifs sont élevées, et associées à un lourd fardeau pathologique et économique. La plupart des troubles répondent de façon satisfaisante au traitement et/ou aux mesures psychologiques, en particulier à la psychoéducation. Le meilleur exemple de cette approche est de loin la série de cours pratiques intitulée « S'Adapter à la Dépression » (*Coping With Depression *[CWD]). Ces cours, largement utilisés dans plusieurs pays, comprennent 8 à 16 sessions qui ciblent les symptômes majeurs de la dépression et l'anhédonie. On peut participer à ces cours à titre individuel ou en groupe ou encore« en solo », selon une approche par auto-soutien guidé. Il s'agit d'une mesure cognitivo-comportementale hautement structurée fondée sur une théorie d'apprentissage social où le médecin est essentiellement un éducateur et les participants sont plutôt des étudiants que des patients ; il n'existe aucune relation psychothérapeutique classique entre les deux. Ces cours sont extrêmement flexibles et peuvent être adaptés à un ensemble de contenus, de populations cibles et de buts y compris au traitement de pathologies établies et en prévention primaire et secondaire. Des études randomisées ont montré que cette approche diminue l'incidence des troubles dépressifs dans la dépression infraclinique, soulage les troubles dépressifs existants et peut aussi réduire le taux de rechute. Elle est aussi plus efficace dans la dépression modérée à sévère, chez les sujets qui en espèrent plus de résultats, qui reçoivent un soutien social plus important et qui se sentent maîtres de leur vie. La dispensation de ces cours par Internet présente de nombreux avantages et devient de plus en plus pratiquée.*

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Pioneering humanitarian medicine

The International Pasteur Institute Network

by C. Régnier, France

Louis Pasteur (1822-1895), a chemist by training, introduced the laboratory into clinical medicine. He was one of the first to understand the need to base medicine, and in particular the study of infectious disease, on a rigorous experimental method. He was a contemporary and friend of Claude Bernard, the founder of experimental medicine. Pasteur also understood that infection could be prevented by clean technique (asepsis) and vaccination. But in a Third Republic where children learned to think of France as having a universal mission by reciting Charlemagne's words from the contemporary play by Henri de Bornier: « *Tout homme a deux pays, le sien et puis la France* — Every man has two countries, his own and France, » Pasteur's vision stretched well beyond France. It made sense only on a planetary scale. If there was to be vaccination, it had to be universal. Hence the need to have production units, research centers, and outposts worldwide. The end of the 19th century was also the era that saw the creation of the first major pharmaceutical companies.

The spirit of this turn-of-the-century age was militantly in favor of spreading scientific knowledge and fighting distant disease such as plague, malaria, sleeping sickness, and leprosy. Bringing the gospel of French science to the world was inscribed in the political ideology of the Third Republic. Colonial expan-

"Science has no country, or rather its country encompasses all humanity." Driven by this conviction, Louis Pasteur urged his students and colleagues, no sooner had they achieved the requisite expertise, to disperse to the four corners of the earth and spread the benefits of French science in response to the huge epidemic challenges of their time. In Paris in 1888, he opened the first Pasteur Institute, a novel institution with a threefold remit, serving as a public health facility specializing in rabies vaccination, an infectious disease research center, and a school of microbiological theory and practice. All Pasteur Institutes that were subsequently set up abroad, in particular in the French colonies from 1891 onwards, were assigned similar objectives. Institute scientists formed a community that was inspired by a philosophy wholly oriented toward research and its practical applications, in particular teaching and the protection of populations threatened by epidemics. Eight Pasteur Institute staff have received Nobel prizes in Medicine or Physiology since 1900. Yet the impetus behind the establishment of many overseas Pasteur Institutes came from the adventurous fieldwork of individual investigators wrestling with a particular problem of infection or epidemiology: Yersin with plague in Indochina, Nicolle with typhus in Tunisia, Laveran with malaria in Algeria, Calmette with snake bites in Vietnam, and Jamot with sleeping sickness in French Equatorial Africa. International Pasteur Institutes now number 30 member institutions, all independent, but bound by a shared scientific philosophy and constituting a network unique in the world.

Medicographia. 2008;30:65-72.

(see French abstract on page 72)

Louis Pasteur (1822-1895) at the London Congress in 1881. © WALERY/ Institut Pasteur.

The historic building of the Pasteur Institute, in Paris (1997). © Service Photo/ Institut Pasteur.

sion and French diplomacy were shot through by a humanism inherited from the French Revolution, revised and updated by the republican public health science of the late 19th century. It was in the name of science that Pasteur's disciples locked step with colonial expansionism in order to spread wide the benefits of medical progress. The first Pasteur Institutes were set up in the humanitarian wake of French colonial expansion and/or in countries which had formed close scientific ties with Pasteur and his earliest pupils.

Founding of the Pasteur Institute in Paris

The impetus came from Pasteur's phenomenal success, in July 1885, in saving the life of 9-year-old Joseph Meister after he'd been bitten by a rabid dog. This was followed by a second successful vaccination in October the same year, performed on a 15-year-old shepherd with even more advanced disease. On the strength of these achievements, on January 12, 1886, Pasteur felt able to write to the Count of Laubespin, a generous philanthropist who had volunteered financial support for his research in the past: "My intention is (…) to establish a model institution in Paris without State aid, thanks to gifts and international subscriptions. I'm confident that a single institution could suffice for France, but also for Europe, Russia, and even North America."

On March 1, at the Academy of Sciences, Pasteur announced that it was urgent to establish a rabies institute, adding: "Clearly, in such an institute, we would need to train young scientists who would export our techniques to these distant lands. We could undoubtedly do likewise for the various regions of Europe." A national and international subscription scheme was launched. It proved immensely successful with heads of state, princes, and those of more modest means, whose names were printed in the French Republic's *Official Journal.* As a foundation in private law, the Pasteur Institute was directed to the public benefit by the decree of June 4, 1887. A subscription of 2 million gold francs enabled it to buy an area of 10 000 m^2 in rue Dutot in the 15th arrondissement of Paris.[1-4] In January 1887, one of Pasteur's old pupils, the biologist and chemist Émile Duclaux, founded the *Annales de l'Institut Pasteur,* a monthly microbiology journal designed to showcase the Institute's work and covering all aspects of the new discipline: medicine, public health, biology, social aspects, and the industrial dimension.[3]

Antirabies vaccination at the "rabies barrier" at the vaccination room of the Pasteur Institute around 1900. © Institut Pasteur.

On November 18 the following year, at the opening of the Pasteur Institute in Paris by the President of the Republic, Sadi Carnot, Pasteur proclaimed the Institute's mission as "at once a health center for treating rabies, an infectious disease research center, and a microbiology teaching center." He filled the five departments of the Institute with scientists having a judicious mix of background and scientific training: two graduates of possibly the most prestigious *grande école,* the *École Normale Supérieure,* Émile Duclaux in general microbiology, and Charles Cham-

berland in the microbiology of public health; a biologist, Élie Metchnikoff in morphological microbiology; and two physicians, Jacques-Joseph Grancher in rabies and Émile Roux in microbiological methods.[2,3,5] The courses on offer established the Institute as a world center of microbiology teaching and a beacon of Pasteurian research. It was also a production and distribution center for sera and vaccines. A steady flow of donations enabled it to expand at regular intervals, building biochemistry laboratories, an infectious diseases hospital (opened in 1900), and an outpatient wing.[4,6,7]

Émile Roux gave the first course, starting in March 1889. It attracted many French and foreign physicians. Each session catered for 40 to 100 students and lasted 5 weeks, in facilities that were remarkably well equipped for the period. The curriculum grew every year and was supplemented by practicals and special lectures. After a gap during the First World War, the courses were reinstated in 1922 by René Legroux and Julien Dumas. Roux was appointed director of the Paris Pasteur Institute in 1904.[4,6,7]

Adrien Loir (1862-1941), a nephew of Louis Pasteur, headed the Pasteur Institutes in Sydney, Tunis, and Bulawayo (Rhodesia). © Institut Pasteur.

Fieldwork and the founding of overseas Institutes

Enterprising fieldwork in Australia, China, Indochina, and North and Sub-Saharan Africa produced some remarkable success stories. Although only made possible by individuals blessed with resourcefulness and intellectual independence of the kind that drove Pasteur himself, these successes also drew heavily upon the reputation of Pasteur the man, his research, his achievements, and the Paris Institute. They included victories over anthrax and pleuropneumonia in Australian cattle, over plague in China and Indochina, and over sleeping sickness in French Equatorial Africa.

In November 1887, the physician Adrien Loir, Pasteur's nephew, tackled the epidemic of bovine infectious disease in New South Wales, Australia. The particular threat was anthrax. Despite going off course several times and underestimating the need to control the rabbit vectors, Loir and his two assistants managed to develop an anthrax vaccine in the laboratories and production center that they set up in 1890 on Rodd Island in Sydney Harbor. Several million head of cattle were vaccinated. Several years later, pleuropneumonia was conquered in Queensland cattle in the same way. By July 1892, the Sydney Pasteur Institute—considered the first of its kind overseas—was producing vaccines against anthrax, glanders, and pleuropneumonia. A year later, however, Loir left Australia for "urgent personal reasons." Disagreements and power struggles between the governors of the different states were almost certainly responsible for his departure. The Australian mission foundered in under 2 years.[3,7]

Alexandre Yersin (1863-1943) in front of the hut in Hong Kong where he discovered the plague bacillus, in 1984. © Institut Pasteur.

No less than four Pasteur Institutes were founded in the French protectorate of Indochina: Saigon (now Ho Chi Minh City) in 1891, Nha Trang in 1895, Hanoi in 1925, and Da Lat in 1936. With each Institute's departments dovetailing with one another, the four institutions were headed by a single director, beginning with Alexandre Yersin in 1904. They had four main objectives: to export rabies treatment throughout the Far East; to produce smallpox vaccine locally (using young buffalo); to study (and if possible eradicate) plague; and to counter the influence of German bacteriology which had already swept through Japan.

Albert Calmette founded the Pasteur Institute in Saigon in 1891 at the insistence of Pasteur and with the support of the Under-Secretary of State for the Colonies Eugène Etienne. It was the first overseas French institute of microbiology. In Saigon, Calmette met Alexandre Yersin; the friendship between Calmette, Roux and Yersin was deep and lasting. The Saigon Institute produced enough smallpox vaccine to immunize all 20 million Indochinese, with supplies left over for nearby China, Macao, and Thailand. Calmette also developed a subspecialty in snake venom antisera production. The Pasteur Institute of Nha Trang opened in a thatched hut along the shoreline in 1895, with Yersin as its first director. The Swiss-French Yersin, whose father died before he was born, started his medical studies in Lausanne and continued them in Marburg, finishing in Paris in 1885. While at the Hôtel Dieu Hospital, autopsying a patient who'd died

Pasteur Institute in Ho Chi Minh City, Vietnam, founded in 1891 by Albert Calmette. © IP Ho Chi Minh-Ville/Institut Pasteur.

Pasteur Institute in Dakar, Senegal, founded in 1923. © IP Dakar/Institut Pasteur.

Hellenic Pasteur Institute in Athens, Greece (1995). © Institut Pasteur.

Pasteur Institute of Iran, at Tehran (1995). © IP Iran/ Institut Pasteur.

of rabies, Yersin cut his finger, and went straight to Pasteur's laboratory in the rue d'Ulm, where he was promptly vaccinated by Émile Roux. This was his induction into microbiology and the start of a long friendship between the three men. In May 1894, Yersin went to Hong Kong at the request of the senator Dr Alcide Treille to investigate the plague epidemic that was also threatening Indochina (it was responsible for 12 million deaths). He arrived on June 15 complete with culture media, microscope, and autoclave. But the British had already called in the Japanese bacteriologist Shiba-saburo Kitasato, a graduate of the German school of Pasteur's personal enemy, Robert Koch. Kitasato's British minders prevented Yersin from taking any samples from the patients in the Kennedy Town Hospital where Kitasato had established his laboratory. Whereas Kitasato was hunting for the plague bacilli—"small stumpy round-tipped rods"—in the patients' blood, Yersin sought them in the lymph nodes and buboes. On June 22, a week after his arrival, Yersin inoculated two mice with homogenized lymph node from the leg of a Mr Olu Kuong, who'd died in the night. From the animals' spleens he was then able to isolate the organism that he named *Pasteurella pestis* in his master's honor, but that since 1970 has been known as *Yersinia pestis* in his own honor. In 1895, he returned to Paris to develop a plague antiserum with Roux and Calmette. He took it back with him to Indochina, set up a manufacturing laboratory in Nha Trang, and trialled his product in the plagues of Canton and Bombay. Yersin went on to establish Pasteur Institutes in Hanoi (1926) and Da Lat (1936), laboratories in Hué (1922), Phnom Penh (1926), and Vientiane (1927), and a journal, the *Les Archives des Instituts Pasteur d'Indochine*, in 1926.[7-9]

Eugène Jamot was a former military specialist in tropical diseases before being appointed director of the Pasteur Institute in Brazzaville (Congo). He set sail for French Equatorial Africa (modern Gabon, Republic of the Congo, Central African Republic, and Chad) on July 13, 1914. In Cameroon, first-hand observation of the havoc, wreaked by sleeping sickness, determined him to overcome trypanosomiasis. Because patients with advanced disease were unable to make their way to the nearest health center, he realized that it was the duty of mobile health care teams to go to them, and specifically to examine every villager living close to the watercourses infested by trypanosomes and the two main species of tsetse fly (*Glossina palpalis* and *G tachinoides*). "Two conditions are needed for the disease to spread across a region and be-

come endemic," wrote Jamot. "On the one hand, the patient acting as the viral reservoir, and on the other, the insect vector." His plan appeared absurdly ambitious: it was to protect villagers against trypanosomiasis by putting in place a policy that combined health education, training of nurses and administrators, the setting up of mobile health care teams, and treatment of those already infected. Jamot's public health program was delivered by mobile teams operating within their defined sectors. On April 12, 1917, Jamot received *carte blanche* from the Governor-General of French Equatorial Africa. Between August 1917 and May 1919, with very modest resources, his mobile teams examined 90% of the population (89 743 inhabitants) over a territory of 100 000 km^2. The results that Jamot presented to the Society of Exotic Pathology were spectacular: decreases of 65% in mortality and 90% in infective risk. He defined the resources required to eradicate the disease: one European physician, three European technicians, and ten African nurses for every 50 000 inhabitants. In March 1922, he settled in Ayos, Cameroon, where in 1925 he set up a training center for doctors, technicians, and nurses.[9-12]

These are just some of the dedicated careers that distinguished the disciples of Louis Pasteur.

Different Institutes bound by a common philosopphy

Pasteur Institute scientists were undaunted in their conquest of new biomedical frontiers. Their aims, in their own minds, were primarily to bring the benefits of French scientific progress to distant populations. Pasteur Institutes were always established in exotic locations in response to some specific public health and infectious problem. Thus, Albert Calmette's mission was to protect the inhabitants of Indochina against rabies and smallpox by vaccination; Adrien Loir's task was to help Tunisian winegrowers to solve problems

The Pasteur Institute International Network

The 30 independent Pasteur Institutes total 10 000 staff in 5 continents:

- **Africa:** Tunisia (Tunis, 1893); Algeria (Algiers, 1894); Madagascar (Antananarivo, 1898); Morocco (Casablanca, 1911); Senegal (Dakar, 1923); Cameroon (Yaoundé, 1959); Central African Republic (Bangui, 1961); Ivory Coast (Abidjan, 1972); and Niger (Niamey, 1978).
- **Americas:** Canada (Laval, 1938); French Overseas Department of Guiana (Cayenne, 1940); French Overseas Department of Guadeloupe (Pointe-à-Pitre, 1948); and Uruguay (Montevideo, 2006).
- **Asia:** Vietnam (Saigon/Ho Chi Minh City, 1891; Nha Trang, 1895; Hanoi, 1923); Cambodia (Phnom Penh, 1913); Iran (Teheran, 1920); China (Hong Kong, 2002; Shanghai, 2004); and South Korea (Seoul, 2003).
- **Europe:** France (Paris, 1887; Lille, 1898); Belgium (Brussels, 1901); Romania (Bucarest, 1901); Greece (Athens, 1919), Russia (St. Petersburg, 1923); Bulgaria (Sofia, 1947); and Italy (Rome, 1976).
- **Oceania:** French Overseas Territory of New Caledonia (Noumea, 1954).

Four of the 30 are associate institutes: the Armand Frappier Institute at Laval in Quebec, the Cantacuzene Institute in Bucarest, the Cenci Bolognetti Foundation in Rome, and the Stephan Angeloff Institute in Sofia.

The Pasteur Institute has also formed partnerships or associations with other foundations or institutes across the world:

- The Weizmann Institute in Rehovot (Israel), establishing in 1975 the Pasteur-Weizmann Council devoted primarily to cancer research.
- The Pasteur Foundation of New York, a company in United States law founded in 1985 to raise funds for the Pasteur Institute.
- The Canadian Louis Pasteur foundation set up in 1997 in Montreal and Toronto, which finances research and grants for young Canadian scientists.
- AMSUD-Pasteur has been developing since 2002 scientific collaboration with Chile and the Mercosur countries (those belonging to regional trade agreement between Brazil, Argentina, Uruguay, and Paraguay), in particular by creating regional biotechnology centers.
- The Oswaldo Cruz foundation in Rio de Janeiro, Brazil, founded in 1902, and which has been exchanging research scientists and collaborating with the Paris Pasteur Institute since 2004;
- The Pasteur Association in Tokyo, which has been financing visits by Japanese researchers to Paris since 2005.

relating to grape juice fermentation; Alexandre Yersin's remit was to overcome human plague. These missions, which today we would call humanitarian, also advanced basic science in bacteriology, virology, immunology, and more generally in medicine. Calmette discovered antivenom serotherapy, and it was by treating typhus patients in the Institute set up by Adrien Loir in Tunis that Charles Nicolle unraveled the role of lice in transmitting the disease.[8,10]

The Pasteur Institute International Network now comprises 30 institutions. Seven Institutes were founded in Africa, Madagascar, and Indochina between 1887 and 1900, ten more in Africa, Indochina, Quebec, Europe, and Russia between 1901 and 1940, and a further seven in Africa, Europe, and the French territories of America and Oceania between 1945 and 1980. Each is independent, with its own history, statutes, specificities, research interests, and challenges.[7] Sometimes it was at the express request of a foreign government, such as in Athens, Teheran, or Shanghai, that the Pasteur Institute was asked to set up a vaccination and infectious disease research center. More rarely, the initiative was private, as in St Petersburg, where the Institute was founded in 1886 with the help of Adrien Loir. But in most cases scientists from the Paris Institute on a mission abroad found themselves involved with, and obliged to respond to, the health service needs of the French overseas civil administration and armed forces. Army doctors such as Jamot were crucially important in establishing and developing Pasteur Institutes in exotic locations abroad, many of which were operated by men of exceptional caliber.[7]

Jean Laigret (1894-1966), in his lab at the Pasteur Institute in Tunis, ca 1935. He developed the first yellow fever vaccination in Dakar. © Institut Pasteur.

The secret of the Network's astonishing durability lies on the one hand in the scrupulous independence of individual institutes from religious or political ideologies, and on the other in the bedrock of ongoing scientific research. The research remit was defined back in 1891 with the creation of the first overseas Pasteur Institute in Saigon: to study the major infectious and endemic diseases in the host country; to improve public health by eliminating epidemics through pathogen identification, vaccination, and treatment; and to train scientists and create a research network linked to the Pasteur Institute in Paris. To quote Pasteur: "Knowledge is humanity's heritage."[1,2,7]

A shared passion for fieldwork united Pasteur scientists, from whatever background. In some cases they returned again and again to a problem until it was satisfactorily solved. Thus, it was on the ground in Hong Kong, in 1894 in the purest Pasteur tradition, that Yersin identified the plague bacillus. In his wake came Paul-Louis Simond, on assignment in Bombay, where he elucidated the routes of transmission of the disease. Later fieldwork by Marcel Baltazard, at the Pasteur Institute in Teheran in 1950, yielded a new preservation method for the plague bacillus and a better understanding of pathogen cyclicity. Finally, it was at the Pasteur Institute in Madagascar that the relationship between plague and changes in the vil-

Pasteur Institutes in the world (as of 2007). © Institut Pasteur.

Chemical analyst at the Louis Pasteur Institute in Brussels, Belgium, testing a sample of salami for the cancer-causing agent dioxin (1999). © Reuters.

Virologist at the Pasteur Institute in Ho Chi Minh City carrying out research work on the mutation of the H5N1 virus (2005). © Dung Vo Trung/dung vo trung/Politika/CORBIS.

Paris Pasteur Institute Center of Scientific Information (1995) built thanks to a legacy from the Duchess of Windsor. © Dacbert, J.-P./Institut Pasteur.

The Paris Pasteur Institute's collection of fungi (2001) the majority of which were isolated from human lesions. © Service Photo/Institut Pasteur.

lage storage of rice was unraveled, and that Georges Girard and Jean-Marie Robic developed the first effective live attenuated vaccine in 1932. As for yellow fever, Jean Laigret, working at the Pasteur Institute in Dakar in the 1930s, developed a vaccine that was to remain the only one of its kind for the next 30 years, while at the Pasteur Institute in Algiers, Edmond Sergent, a settler Algerian from Philippeville (modern Skikda), designed the country's malaria prevention program in the 1920s.[7-9]

Some Pasteur scientists complemented their research by becoming anthropologists, ethnologists, or sociologists in the belief that a better understanding of indigenous behavior with respect to infectious diseases would inform their preventive strategies. A notable example was Army doctor Émile Marchoux in his studies of yellow fever, typhoid, and malaria in Brazil and Sub-Saharan Africa in the early 1900s.[7]

The Pasteur Institute Network: a history that is written daily

Prior to 1970, Pasteur Institutes appeared isolated, without real contact with one another. Their only real relationship seemed to be with the Pasteur Institute in Paris. Then in 1972, at the instigation of Pasteur scientist Jacques Monod, winner of the Nobel Prize for Medicine in 1965, a council of Pasteur Institute directors was established, with striking results. With its annual meeting and associated networking, the council instilled an awareness into each member of their shared intellectual and human heritage and the need to keep it healthy. At the same time, it gave rise to the concept of an international Pasteurian scientific community. The name "Overseas Pasteur Institute" no longer seemed appropriate in this new conceptual framework, and it was replaced in 1988 by that of "International Network of Pasteur Institutes and Associate Institutes" (RIIP, Réseau International des Instituts Pasteur)

In the 1980s, study groups were set up to incorporate all those within the community who were involved in a particular line of research. Thus the virology group sprouted subgroups classified by their pathogen of interest: arbovirus, polio enterovirus, human immunodeficiency lentivirus, human T-cell leukemia virus, etc.

In recent years, the multipartner regime has been formalized in a General Declaration of Scientific Cooperation signed by all Institutes and, more recently, in a Network Charter, which determines the membership of each Institute within the Pasteurian community, with the statutory election to the Assembly (the highest authority in the Paris Pasteur Institute) of twelve Institute directors chosen by their peers. This reform reflects the determination of the Paris Institute to incorporate Network members in its administration. 1991 saw the creation of the Calmette Fund, which awards training or exchange scholarships, while an inter-State ranking commission independently monitors the careers of national researchers. Functioning in a few Institutes only, this consultative commission could see its role expanded in response to increased demand. The creation of a Network scientific committee to act as a think-tank for the Director-General further enhances interaction both within the Network and between the Network and the Paris Institute, while also promoting the Network's potential. Various measures are also in the pipeline for accelerating information exchange within the Network.

Above all, however, the Pasteur Institute Network is a collective enterprise driven by high-caliber individuals drawn from different cultures,but bound by the same faith in scientific method, and by a tradition cemented on the one hand by the day-to-day problems encountered by scientists in their research and on the other by the philosophy bequeathed to them by Pasteur himself. Still thriving after well over a century of complete independence, the Network continues to be the world's only such collective scientific enterprise. ❒

REFERENCES

1. Balbar F, Prévost ML. *Pasteur: Cahiers d'un Savant*. Paris, France: CNRS–Bibliothèque nationale de France; 1995.
2. Dagognet F. *Pasteur Sans la Légende*. Paris, France: Les empêcheurs de penser en rond; 1994.
3. Debré P. *Louis Pasteur*. Paris, France: Flammarion; 1995.
4. Dubos R. *La leçon de Pasteur*. Paris, France: Albin Michel; 1987.
5. Pasteur L. *Écrits scientifiques et médicaux*. Paris, France: Garnier-Flammarion; 1994.
6. Dubos R. *Louis Pasteur*. Paris, France: La Découverte; 1995.
7. Morange M. *L'Institut Pasteur: Contributions à son Histoire*. Paris, France: La Découverte; 1991.
8. Brisou B. Les pionniers de la peste, médecins coloniaux et pasteuriens: Yersin, Simond, Girard et Robic. *Hist Sci Méd*. 1995; 29:327-336.
9. Jason M. *Les débuts de la Médecine Française au Sud-Viêt-Nam, au Cambodge et au Laos à la Fin du XIX*e *siècle*. Paris, France: Doctor of Medicine thesis 972; 1962.
10. Bebey Eyidi M. *Le vainqueur de la maladie du sommeil: Le docteur Eugène Jamot (1879-1937)*. Paris, France: Bebey Eyidi; 1951 (extracts: http://medecinetropicale.free.fr/cours/jamot.htm).
11. Jamot E. La prophylaxie de la maladie du sommeil. In: Bernard N, Blanchard M, Cazanove F. *Les Grandes Endémies Tropicales; Études de Pathogénie et de Prophylaxie*. Paris, France: Vigot Frères; 1930.
12. Raichvarg D. *Louis Pasteur, L'Empire des Microbes*. Paris, France: Découvertes Gallimard; 1995.

Le réseau international de l'Institut Pasteur, pionnier de la médecine humanitaire

« La science n'a pas de patrie, ou plutôt la patrie de la science embrasse l'humanité toute entière. » Fort de ce principe, Louis Pasteur engagea rapidement ses élèves et ses collaborateurs à essaimer à travers le monde pour répandre les bienfaits de la science française et pour répondre aux grands défis épidémiques de son temps. Le premier Institut Pasteur fut inauguré à Paris en 1888. Cet établissement d'un genre nouveau devait poursuivre trois missions: les soins et les vaccinations contre la rage (dispensaire); les études sur les maladies infectieuses; l'enseignement de la microbiologie. Ces mêmes objectifs furent assignés à tous les Instituts Pasteur qui furent installés à l'étranger, en particulier dans les colonies françaises, dès 1891. Les Pasteuriens formèrent une communauté scientifique animée par une philosophie entièrement tournée vers la recherche, la diffusion des découvertes et la protection sanitaire des populations soumises aux fléaux épidémiques. Huit chercheurs des Instituts Pasteur ont reçu depuis 1900 le prix Nobel de Médecine ou de Physiologie. Pour autant, la fondation d'Instituts Pasteur hors de France fut avant tout le fait d'aventures individuelles de Pasteuriens captivés par la résolution d'une question infectieuse ou épidémiologique: Yersin en Indochine (la peste), Nicolle en Tunisie (le typhus), Laveran en Algérie (le paludisme), Calmette (les morsures de serpent), et Jamot en Afrique centrale (la maladie du sommeil). Aujourd'hui, le réseau des Instituts Pasteur rassemble une trentaine d'établissements à travers le monde. Indépendants mais liés par une philosophie scientifique commune, ces Instituts constituent un réseau unique au monde.

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The Alliance Française

Bringing French language and culture to the world

by J.-C. Jacq, France

> **"On ne résiste pas à l'Alliance Française"**
> **Charles de Gaulle**
> 2 December 1958 *(75th Anniversary of the Alliance Française)*

One July Saturday in 1883, as the plane trees along the boulevard Saint-Germain in Paris struggled to contain the blazing afternoon sun, a handful of men in suits and hats braved the heat in the meeting rooms of the Saint-Simon Circle history society to learn more about an ambitious new project being put forward by its two advocates: the diplomat Paul Cambon, the future French ambassador in Madrid, Constantinople, and London, and Pierre Foncin, a geographer with a passion for the high seas and international relations. Those seated around the table represented a broad secular and religious spectrum of what today we might call education stakeholders: the former Minister of Education Paul Bert, two senior civil servants from the Ministries of Foreign Affairs and Education, the apostolic missionary Father Charmetant, the Saint-Simon Circle's treasurer, Alfred Mayrargues, a Jew, and an academic, Paul Melon, a Protestant. This patchwork little group could have had little idea that what it was bearing to the baptismal font has since grown into the world's largest cultural nongovernmental organization.

For these enlightened patriots the underlying agenda was to restore the international prestige of France after the battering it had taken from the Prussians at Sedan in 1870. How? By setting up "a national association for propagating the French language in the colonies and abroad."

July 1883 saw the birth in Paris of "a national association for the propagation of the French language in the colonies and abroad." The Alliance Française, a cultural movement that enjoyed a brilliant career in a 20th century scarred by the eclipse of humanism, is striding into the 21st century in better health than ever and bursting with new projects. It functions according to three principles that were spelled out at its inception and have remained astonishingly modern ever since. The first, rooted in the period, was the idea of restoring French prestige, sorely undermined by the defeat of 1870 in the Franco-Prussian war, using the peaceful weapons of language and culture, ie, by cultural influence rather than by war. The second, virtually without precedent in France, was to rely on a non-State association to conduct a policy of international influence. The third was to entrust the cultural and linguistic promotion of France to foreigners. Alliances worldwide are associations in local law, headed on a voluntary basis by local nationals with a love of French culture. The concept has proved extraordinarily successful. From Canada to Tierra del Fuego, South Africa to the edge of the Artic Circle, Russia to India, and China to Oceania, over 1000 Alliances now cater for 450 000 students and over 6 million visitors to their cultural displays and events. A Foundation set up in 2007 underwrites the future of this remarkable enterprise and helps to promote cultural diversity worldwide.

Medicographia. 2008;30:73-83. *(see French abstract on page 83)*

Jean-Claude Jacq, Secretary-General of the Alliance Française, Paris, France. Photo courtesy of the author.

Jean-Claude Jacq *is a Sciences Po graduate and holder of the highest competitive teaching qualification, the* agrégation, *in French language and literature. After teaching at Mohammed V University in Rabat, Morocco, he became Director-General first of the Alliance Française in São Paulo, Brazil, then of the Paris Alliance Française in Portugal. In 1993, he was appointed Cultural, Scientific, and Cooperation Advisor to the French Embassy in Israel, and Director of the French Institute in Tel-Aviv. Four years later, he was made Deputy Director of Social, Human, and Archeological Sciences at the Ministry of Foreign Affairs. He was elected Secretary-General of the Alliance Française in September 2001. As Vincent Jacq, he has written a number of books, including* Odeur d'Encre, Odeurs d'Îles *(Paris; Julliard: 1991), given talks on the France-Culture radio channel, and written for* La Quinzaine Littéraire, *the* Monde Diplomatique *and the journal* Levant. *Since 2002, he has also been Deputy Chairman of the French National Commission's Social and Human Sciences Committee at the United Nations Educational, Scientific, and Cultural Organization (UNESCO).*

The ambition of using education to promote progress dovetailed quite naturally with the expansionist drive that gripped France at the turn of the 19th century. There was, of course, much more to that drive than the advancement of education, but education was its generous and humanist face, expressed in the unabashed proclamation of civilizing pretensions, however politically incorrect these may sound to modern ears. But we have only to look at other cultures in other eras—Mesopotamia under Hammurabi, Greece under Pericles, China under the Tang, Rome under Marcus Aurelius, or indeed France itself during the Enlightenment—to realize that they too were similarly convinced of their moral, esthetic, and spiritual excellence, and of the exemplary level of their social and political development. Comparison with such peak periods in cultural achievement does not appear unwarranted. French creativity had perhaps never been as intense and wide-ranging as at this time in its history. In 1883, its greatest creators were in their prime: Cézanne was 44, Monet 43, Zola, Renoir, Verlaine and Fauré were approaching 40, while the young guard was represented by no less than Gauguin, Van Gogh, and Debussy. Rimbaud was in Harar, Ethiopia, while his work was being published by Verlaine, Pasteur was performing some of his most important work in Paris, and Delamare-Debouteville was inventing the modern automobile.

The Alliance Française building in Paris. © Alliance Française.

The history of the Alliance is interesting in that it represents a sort of protohistory of French international cultural policy. Until that time, cultural policy was unofficial, conducted in only a few regions of the world, albeit with considerable influence, by a few thousand missionaries representing a variety of religious persuasions, and accessorily, since its founding in 1860, by the Alliance Israélite Universelle. What was special about the Alliance Française was that it represented the emergence of a nondenominational institution inspired by scientists, writers, politicians, and businessmen aiming to undertake concerted activity on a global scale.

Founding principles

From the outset, despite the radical differences in ideological context between that era and our own, there were three founding principles that continue to make the venerable Alliance an astonishingly modern institution, even by today's standards.

The first such principle—surprising in a country that always expects so much from the State—was the idea of relying on a non-State association for developing and implementing a policy of cultural and educational influence abroad. The boldness of this initiative has always been the most striking feature of the Alliance, but, depending on one's degree of belief in the merits of central control, it has also been its most admired and most contested feature, informing the Alliance's ambiguous yet fruitful relationships with the authorities throughout its long history.

The second principle was that of recruiting the charm of French culture to compensate for military failure. The idea of erasing defeat on the battlefield through a combination of exhibitions, concerts, and language courses was most unusual. How much suffering would countries had been spared had their battles been confined to quarrels between grammarians (however vicious these may be) or the fist-fights between Romantics and Classicists on the opening night of Victor Hugo's *Hernani?*

Pierre Paul Cambon (1843-1924), who conceived the concept of the Alliance Française. A French diplomat, with postings in Tunis, Madrid, Constantinople, and London, he signed with Lord Lansdowne the *Entente Cordiale* convention between France and Britain in 1904 and helped resolve the Balkan Wars crisis between 1912 and 1913. © Alliance Française.

The third and probably most revolutionary principle was that of Frenchmen entrusting the cultural and linguistic promotion of their country to foreigners: as "free associations of free men," the various Alliances throughout the world are associations in local law that are staffed and operated by local nationals with a love of French language and culture.

Of all the major cultural organizations with an international vocation—British Council, Goethe Institute, Cervantes Institute and, more recently, Confucius Institute (all established at later dates)—the Alliance Française is alone in operating according to such a model. The Alliance is only French in France. Elsewhere it is American, Bulgarian, Kenyan, or Korean. The Paris Alliance, which launched the basic idea of the institution and laid its foundations, provides long-term support, ensures consistency across the movement, including compliance with its statutes, and helps to recruit staff seconded to the various Alliances by the Ministry of Foreign Affairs.

From the outset, the founders excluded all sectarian and party bias and all political, religious, and ideological commitment. They appealed to people of goodwill from across the opinion spectrum, to all those enamored of the French language and concerned for its future—industrialists, merchants, shipowners, chambers of commerce, learned societies, journalists, economists, and the like—in fact to all those interested in French expansion across the world under the exclusively peaceful guise of its language and culture.

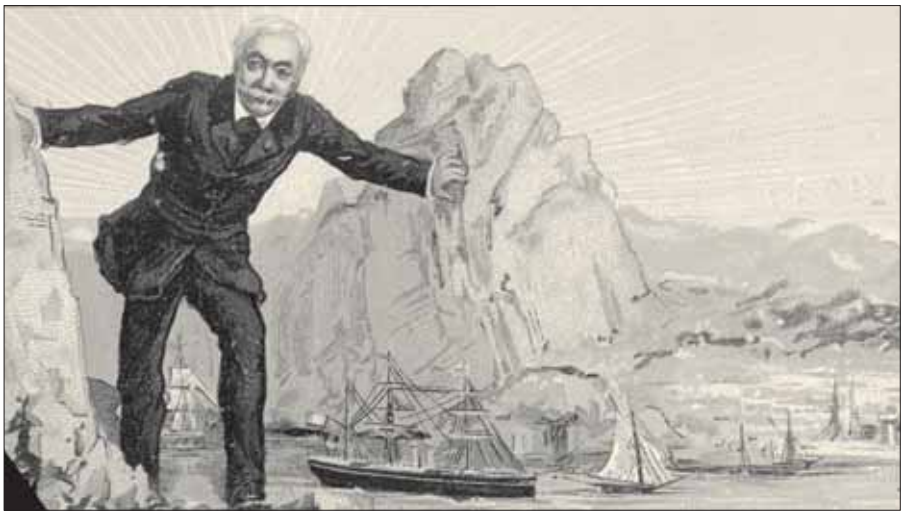
These powerfully principled ambitions captured the immediate attention of some important public figures: the explorer Savorgnan de Brazza, Cardinal Lavigerie, the Egyptologist Gaston Maspero (founder of the Cairo Museum), the medievalist Gaston Paris, the writers Ernest Renan and Hippolyte Taine, General Faidherbe, and Louis Pasteur. A board of directors was set up that included men from the most varied backgrounds: diplomats and academics sat alongside archeologists (Salomon Reinach), historians (Ernest Lavisse, Victor Duruy), geographers, magistrates, and publishers (Armand Colin), while religious figures (Pastor Puaux, Chief Rabbi Zadoc Kahn) rubbed shoulders with determined anticlericalists such as Paul Bert. The association was registered on January 24, 1884, thereby officializing the birth of a venture that was to extend to all five continents and survive all the trials and tribulations of a particularly event-laden 20th century.

French geographer Pierre Foncin (1841-1916), the first Secretary-General of the Alliance Française, from 1883 to 1897. © Alliance Française.

A dazzling debut

Active committees sprouted across France in response to public lectures by academics such as Jean Jaurès ("the Alliance Française can count on people flocking to it from every corner") or the economist Charles Gide, uncle of the writer. Jules Verne himself set up an Alliance in Amiens, while the future head of government Casimir-Périer founded another in Troyes. Membership applications flowed in from many countries, with committees being set up in London, Barcelona, Tangiers, Fez, Tunis, Tokyo, Constantinople, and Mexico City. But fastest of all off the mark was Mauritius, known as Île de France before the British takeover: the Port Louis committee met as early as September 1884, offering French lessons, granting scholarships, organizing concerts and celebrations, and launching an annual French language competition that remains immensely successful to this day.

The association was registered as being of public benefit in 1886 and the Suez Canal engineer, Ferdinand de Lesseps, became its chairman in 1887. Pierre Foncin, the first Secretary-General, was the effective architect of the association. His first concern lay with the countries closest to home, the Maghreb, and Algeria in particular: "How many of the 20 000 school age Muslim children are being educated in French? 6000. Is that worthy of a great nation?" The Alliance funded schools, distributed books, provided grants, and set up its first courses for North-African adults. In Black Africa, the Alliance established thirteen schools in Senegal. Local associations were set up on Réunion Island, in Madagascar, and even Zanzibar. Others followed in the Eastern Mediterranean and Middle East (Greece, Turkey, Persia, and Egypt). The



Ferdinand de Lesseps (1805-1894) a diplomat who after his success in developing the Suez went on to head ill-fated attempt to dig the Panama canal, was the second President of the Alliance Française, from 1887 to 1888. He is shown here, in a caricature, pushing away the mountains to make way for his canal. © Roger-Viollet.

Alliance supported many French-speaking schools, regardless of denominational or nondenominational status. It has always been very French in its commitment to secularism, remaining steadfastly neutral and respectful in all matters pertaining to religious belief. In Asia, it was only natural for the Alliance to establish its first outposts in regions where France already had a stake, such as its renowned trading posts in India (Pondicherry [now Puducherry], Karaikal, and Chandernagore [now Chandannagar]), and the countries of Indochina. But associations were also set up in Canton, Peking, and Shanghai. The first Australian committee met in Melbourne in 1890.

The Alliance appointed a General Director in Montreal in 1885. Pierre Foncin told Canadian deputy minister Monsignor Lavelle: "Be sure to tell our brethren that from now on we shall no longer forget them and that we love them with all our heart." In the United States, Franco-American friendship societies applied to affiliate with the Alliance, which set up in New York and San Francisco.

In Latin America, which in the 20th century was to become the Alliance flagship, committees sprang up in Mexico City (1885), Costa Rica, and Cuba (1886), but also in Caracas, Montevideo, Lima, Mendoza, and Tucuman. The Rio de Janeiro Alliance was founded in 1886 and a local newspaper wrote: "we shall be seeing institutions on every side that regardless of nationality, age, sex, circumstances, resources, color, or race will offer free tuition in the language in which the rights of man were first written."

In 1889, the Alliance Française was present at the Universal Exhibition in Paris, where it was awarded a Grand Prize, as well as three gold and five silver medals for the schools it was supporting. It should be said that the Paris headquarters was supporting these schools with annual subsidies to the tune of over 100 000 gold francs. Such sums were raised by public lectures, balls, parties, lotteries, charity sales, and of course banquets (in the finest restaurants—Ledoyen, Le Grand Véfour, etc), and even by door-to-door collections. The regional councils and Ministry of Foreign Affairs decided very early on to support the undertaking, with the Ministry in particular proving the Alliance's most faithful partner over the years, along with the Ministry of Education. Beginning in 1894, a monthly newspaper was published aimed at younger readers to inform them about "other peoples, their customs and ways of life, the progress they are making, the instructive examples they offer us, and about their children and schools." This concern for knowledge about other cultures, and the taste for what today we term cultural diversity, were fundamental to the Alliance Française from the outset and probably one of the keys to its success.

Poster advertising an "artistic and literary matinee" in support of Madagascan schools, organized in Paris by the Alliance Française in 1898. © Alliance Française.

In the years following, the Alliance developed the broad outlines of a thoroughly modern cultural policy. It devised lecture tours and adult language courses, funded book publications and scholarships for foreign speakers, and networked with local individuals and organizations. As the historian François Chaubet has written: "It will be difficult to reimburse at their true value the drafts drawn by the apparatus of 20th century cultural diplomacy on the operational methods developed by the Alliance."

"The bright flame of French thought"

Such was the Alliance's expansion, both abroad and within France, that the association decided in 1913 to treat itself to prestigious headquarters, purchased from the University of Paris, at 101 boulevard Raspail, thanks to help from a number of publishers, including Armand Colin, Flammarion, and Hachette. Over 12 000 students of French now pass through the building annually. It has a theater, auditorium, and gallery, as well as a remarkable resource center and multimedia library.

The cultural diversity issue

The advent of globalization has brought the issue of cultural identity and its future into much sharper focus. This is not a new phenomenon, if we think back to the great empires of past millennia. But the new communication techniques make today's globalization different. Images, and the means by which they are transmitted and displayed, have become universal, and they express, despite themselves, the primacy of economic dominion that shapes our era.

Attempts to preserve the greatest possible cultural diversity for the future give rise to a multiplicity of issues relating to geopolitics, citizenship, artistic expression, economics, technology, and ecology, to take but a few that arouse enormous tension.

It's doubtful whether the market can be trusted to safeguard cultural and linguistic diversity, since with a rationale of effective production at lower cost, it inevitably entails a degree of standardization. Culture, on the other hand, more than any other "good," has a symbolic dimension that greatly transcends the use-value of goods or the contribution of cultural production to the gross domestic product. That is why the United Nations Educational, Scientific, and Cultural Organization (UNESCO) approved the Convention on the Protection and Promotion of the Diversity of Cultural Expressions on October 20, 2005 by 148 votes to 4, and 4 abstentions. This was no mean victory. The Convention's purpose is important: it seeks to guarantee, in the cultural area, the freedom of States to define and conduct policies that preserve the diversity of their cultural expression.

The Alliance Française sees as its vocation to campaign along the same lines. It is convinced that the current situation, in which there is a virtually obligatory universal language, creates effective inferiority in intellectual and scientific discourse in all those who are not that language's native speakers. This could lead to a pernicious form of sterilization of research. The Alliance is convinced that monoculturalism could ultimately prove highly detrimental to the capacity of innovation and that it could also make life so monotonous that it would be scarcely worth living.

That is why the Alliance devotes so much energy to showcasing the cultures that host its many outposts: exhibitions and concerts in the host countries and Paris, publications, studies, backing for the Maison des Cultures du Monde, week-long cultural festivals at the Paris headquarters, etc.

After surviving the painful interlude of the First World War, the Alliance gained in strength, chaired or operated by major political figures, including some future presidents of the Republic, such as Raymond Poincaré (twice chairman of the Alliance), Paul Deschanel, and Paul Doumer. The schools subsidized by the Paris headquarters or provincial committees were numbered in their hundreds. There were around 200 committees in the United States. In 1921 the new Soviet regime allowed the Moscow Alliance to remain open. Pupil numbers continued to grow in Alliances worldwide, whether in Mexico City, Buenos Aires, Shanghai, or Sydney. New centers were set up in Czechoslovakia, Poland, Canada, Egypt, and Syria. In Paris, leading figures came on board, including the sinologist Paul Pelliot, the sociologist Lucien Lévy-Bruhl, the writer André Maurois, the lawyer Maurice Garçon, and General Gouraud. But the 1929 Crash had a severe impact on the international network and encouraged the growth of nationalism, in particular in the countries that were established or reestablished after the World War. Pupil numbers in the various Alliances declined, and financial difficulties rose to the fore.

The Roaring Twenties finally clouded over. Following the Munich agreement, the Paris headquarters received a "sorrowful message" from the chairman of the federation of Czech Alliances, to which Georges Duhamel, elected chairman in 1937, could respond only with embarrassed sympathy.

By 1940, the Germans had become masters of Paris. They ordered the closure of the Alliance, viewing it as a potential hotbed of moral resistance, and dispatched its archives to Berlin, where they were carefully scrutinized, probably for political purposes. They were later confiscated by the victorious Russians and shipped to Moscow, from where they were only repatriated to the Paris Alliance in October 2000. Although severely depleted, they still contained handwritten letters by, among others, Marcel Proust and Louis-Ferdinand Céline.

Today's Alliance Française network

Student numbers are growing by approximately 5% annually. Growth is highest in the major countries, such as China, India, the United States, Canada, Mexico, Russia, Brazil, Congo, South Africa, and Angola, suggesting that French is far from a marginal demand.

Latin America, with 125 000 students, is the world's largest network, led by Brazil and Mexico, but followed closely by Colombia, Peru, and Argentina. The largest Alliances are to be found in Lima, Bogota, São Paolo, Mexico, Rio de Janeiro, Buenos Aires, Monterrey, and Quito. They are extremely active on the cultural front, often bravely so, such as in Medellin, Colombia, where the Alliance puts on classical music concerts in hospitals, orphanages, and shanty towns rocked with violence.

Europe is the second largest network, with 84 563 students, but is to some extent the victim of the monolingual bias in European Union institutions. In Central and Eastern Europe, since the fall of the Berlin Wall, the Alliance has grown in strength, and has opened numerous branches in Russia, in Nizhny Novgorod, Samara, Ekaterinburg, Rostov-on-Don (set up by the cellist, Mstislav Rostropovich), Novosibirsk, and soon Irkutsk.

Asia, with 81 810 students, is proving remarkably dynamic. India has the largest network (24 000 students), followed closely by China, where numbers are growing by 12% annually. The longest established Alliances are in Hong Kong and Macao, but in the last 10 years others have been set up in Shanghai, Canton, Beijing, Wuhan, Chengdu, Nanjing, Xi'an, Dalian, and Qingdao. Asia also has other great Alliances to its credit, of course, such as in Singapore, Bangkok, and Seoul. The 31 Alliances in Australia cater for 7600 students (a 16% increase). The French Film Festival organized by Sydney and the French Festival in Adelaide are the two landmark events in the country-continent's French cultural calendar.

In Africa and the Indian Ocean, Madagascar heads the field (25 317 students), followed, among others, by Nigeria, South Africa, and Kenya. Numbers tend to be growing in all the anglophone countries wanting to do business with francophone countries "in the neighbor's language."

Both great North American networks are showing significant expansion: Canada has 12 860 students and the United States over 20 000, with major centers in Toronto, New York, and Miami. To consolidate their futures, Alliances have embarked on a vast building movement, thanks to the French Ministry of Foreign Affairs, which is generously topping up the investments made by the committees themselves. Building is currently going on in Madagascar, La Paz, Kampala, New Delhi, Miami, Lima, and Bogota, and restoration works in Dublin, Rio, Bangkok, Karachi, and Trujillo, among other locations.

Alliance Française centers in the world (2007). Tthe Alliance Française currently operates 1071 centers in 133 countries on all five continents. Every year more than 450 000 students take language courses and 6 million persons attend cultural events organized by the Alliance Française. © Alliance Française.

Following the closure of the Paris Alliance, the British federation agreed to a request from the Paris board of directors to take over and manage the world network. It was a fine example of just how resilient this large movement could be. General de Gaulle agreed to act as honorary chairman of a governing board in London and congratulated the Alliance on having been "the first society to have rallied to the Free French cause and placed its organization at its service." This marked the start of de Gaulle's unfailing benevolence toward the institution. On October 30, 1943, in Algiers, General de Gaulle gave a magnificent speech to mark the 60th anniversary of the founding of the Alliance française: "How was the bright flame of French thought able to have acquired and maintained such sparkle, unless fed so liberally by other countries' genius? I have drawn the conclusion once and for all that it is only by unfettered intellectual and moral communication between ourselves and others that our cultural influence can expand to everyone's advantage and conversely heighten our own worth." He went on to add: "Organizing this communication was the founding principle behind the Alliance Française; it remains its reason for being, and will be the reason for the Alliance continuing with its work."

Mauger's *"French Language and Civilization Course,"* the first Alliance Française language course book, published in 1953, was an instant success and sold over 2 million copies, with reeditions into the 1980s. © Alliance Française.

Hall of fame: German top model Claudia Schiffer was once a student at the Alliance Française. Other famous alumni include Colombian author Gabriel García Márquez; Italian actress Gina Lollobrigida; Japanese fashion designer Kenzo; former Empress of Iran Farah Diba; Giovanni Montini, later Pope Paul VI; German movie actress Hanna Schygulla; Russian chess player Boris Spassky; US movie actor Robert de Niro; US-born opera singer Barbara Hendricks; Greek composer Mikis Theodorakis; and many others. © CORBIS.

Reconstruction

The Alliance faced tough challenges in recovering from the war years. Its coffers were empty, its archives in Russian hands, and its network a shadow of its former self (pupil numbers were down to just 14 000). On top of which, its very existence was threatened at home by certain senior civil servants who dreamed of replacing it with a State network more in line with French administrative tradition. Furthermore, French prestige had been seriously undermined by defeat, occupation, and exclusion from the Big Three Yalta Conference. The combined effect of these factors on an institution wholly given over to promoting the influence and cultural signature of France was enough to make anyone despair. But the arrival of Marc Blancpain as Secretary-General, first to chairman Georges Duhamel, then soon afterwards to Émile Henriot, marked the start of an irresistible climb back from the brink. Marc Blancpain was a master builder. His decades at the head of the institution (Secretary-General from 1944 to 1978, then chairman from 1978 to 1993, totaling half a century at the head of the organization) left a deep imprint on both the spirit and practice of the Alliance in France and worldwide.

Under the Blancpain leadership, the Alliance instituted an energetic book policy, combined with the introduction of new teaching methods. It developed its own textbook with a distinctive blue cover that became known to thousands of students worldwide by the name of its author, Gaston Mauger. Alliances throughout the world were strongly encouraged to invest in property as the only bulwark against the vicissitudes of history. The Paris headquarters were extended, but buildings also went up in Brazil, Chile, Peru, and Mexico thanks to support from the Ministry of Foreign Affairs. New faces on the board of directors included the psychiatrist Jean Delay, the then minister for Overseas Territories François Mitterrand, the philosopher Gaston Berger, the physicist Louis Leprince-Ringuet, the poet and president of Senegal Léopold Sédar Senghor, and Wilfrid Baumgartner, the then Governor of the Bank of France who subsequently, after leaving office as Minister of Finance in 1962, was to prove a remarkable Alliance President until his death in 1978.

International activity and the Paris School expanded to such an extent that in 1952 a major building program was undertaken to establish a hall of residence for around 100 students from the world over to come and study French in Paris. This was supplemented by further new buildings on land purchased in 1961 to enable the School to cater for close on 30 000 students annually. How many future celebrities on arriving in Paris have since discovered their affinity for the French language thanks to the Alliance? Among our contemporaries they include the painter Zao Wou-Ki, the writers Hector Bianciotti and François Cheng, who have both been elected to the French Academy, and Claudia Schiffer and Kenzo from the world of fashion.

To mark the institution's 75th anniversary, in December 1958, General de Gaulle gave a speech, this time at the Paris headquarters, that included the since-famous phrase: *"On ne résiste pas à l'Alliance Française"* (one cannot resist the Alliance Française). Modeled in language and sentiment on a celebrated maxim by Victor Hugo on the superiority of ideas over armies, what de Gaulle had in mind was that the strength of the Alliance lay at a level at which all resistance was futile. "For me," he explained, "the Alliance Française represents a permanent ambassador for what lies above and beyond politics. It transcends the mundane; it operates above difficulties, divisions, and criticism. It is the ambassador of all that is modern in the actions of France."

The three boom decades following the Second World War were good for the Alliance too. Its centers became dotted over the five continents, thanks also to the new luster that France had started to acquire. Politically committed intellectuals, daring architecture, and undisputed supremacy in the fashion world leveraged the reexpansion of the Alliance, along with films and popular songs that somehow managed to be hits both at home and across the world. In addition, Philippe Greffet, who was appointed secretary-general in 1978, obtained enthusiastic backing from the Ministry of Foreign Affairs: as a result, in the 1980s, the number of expatriates seconded to head local boards of directors increased to almost 500. This was an opportunity for the young teachers concerned to discover multiple facets to their calling: they were just as likely to have to equip a building or repair an aging roof as to plan lessons, recruit colleagues, set themselves a budget, manage staff, or advertise their Alliance's events. They became transformed almost overnight from civil servants into heads of small companies. Their other duties were to welcome visiting lecturers, organize dinners, prepare shows and exhibitions, showcase films, and work on projects with local partners, in every case with a great measure of freedom and unhampered by bureaucratic inertia. Most of those given such opportunities became disinclined ever to work under different conditions.

In 1982, partnered by the Ministry of Culture, the Alliance set up, at its Paris headquarters, the Maison des Cultures du Monde, which for the last 25 years has been introducing the French public to the most authentic and diverse expressions of artistic inspiration from around the world (www.mcm.asso.fr). At the 1983 centenary attended by some 400 national and international delegates at the Comédie Française, President Mitterrand paid tribute to "the Alliance Française, this exceedingly rare combination of experimentation and tradition, which adds grandeur and beauty to our lives."

Alliance Française Center in Calgary (Alberta), Canada.
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Alliance Française Center in Quito, Ecuador.
© Alliance Française.

What are the ingredients of the combination?

The several ingredients begin with the way in which the Alliance is organized. The network does not operate hierarchically. Perhaps the closest model is that of a neuronal network, ie, a constellation of elements in continuous interaction, yet each remaining autonomous while freely attached to the network. This explains why all the Indian, Canadian, Brazilian, Chinese, or Ghanaian administrators, for example, feel themselves to be fully responsible for their local associations and why they probably put far more energy into running them than they ever would on behalf of an employer or institution reporting to another State.

Among other ingredients is the Alliance's unique capacity for integration. The very fact that it is an institution in local law operated by local citizens effectively involves each Alliance in the hopes and high points of the host society, but also in its political and social hazards. There are any number of examples. During the years of military repression in Latin America, when all intellectual and artistic activity was banned, the Alliance was a haven for the intellectuals, students, and artists who were preparing their countries' futures and who, later, were to be generous in making their gratitude known. The serious economic crisis that struck Argentina early this millennium did not spare the Buenos Aires Alliance, but it has since got back

Cultural event in Bangalore, India. © Alliance Française.

Bastille Day celebration at the Alliance Française Center in Washington, DC: period costumes from the French Revolution. © Alliance Française de Washington DC.

onto its feet, along with the country itself. Although the war in Afghanistan has led to the closure of the Alliances in Pakistan, the premises and activities of those in Madagascar remained untouched throughout the disturbances—in particular, the anti-French movements—that marked the last presidential elections in this country. Why? Because they were seen as Malagasy, not French. The same applied when France fell out with the United States over the invasion of Iraq. The American Alliances were able to trade on their home-grown patriotic legitimacy to curb local tempers and keep relations on an even keel for the future, while in Paris the Alliance held high the torch of friendship between peoples, over and above transient differences, however bitter these might be.

Integration is not an empty word. The readiness of the Alliances in the Indian Ocean to pitch in alongside the local authorities after the tsunami in December 2004 gives an even better understanding of why local populations can feel so strongly attached to "their" Alliances. Both the Bangkok and Colombo Alliances set up emergency reception centers for the stricken populations and coordinating centers for the aid services. This shoulder-to-shoulder solidarity by an institution embedded in the surrounding social fabric is without doubt one of the Alliance movement's moral beauties, and perhaps its deepest *raison d'être*.

A final ingredient worth highlighting is the flexibility of the Alliance formula, its "off-road" capability. Being apolitical and nondenominational, the Alliance can adapt to virtually any social environment: it can set itself up in Vancouver just as readily as in Bangui in the Central African Republic, or as in Medellin, or Ulan Bator; it's as comfortable in the township of Soweto as in the swish sections of Washington or Boston, or in the outskirts of Calcutta as in the port city of Rotterdam. Climatic extremes are no deterrent: the southernmost Alliance outpost is in Ushuaia, in Tierra del Fuego, and its northernmost in Skellefteå, in northern Sweden, at the edge of the Arctic Circle.

The Alliance's current missions

During Jean Harzic's term as Secretary-General from 1988 to 2001, and subsequently, commitment to the Alliance ideals remained strong and it has continued to expand worldwide, despite a sharp decrease in the resources earmarked for cultural activity outside France and a consequent drastic reduction in State support. The traditional missions of the Alliance (French teaching, cultural exchange, and the provision of documentary resources) still constitute the "hard core" of its activities, but they have adjusted to some contemporary developments. The combination of a globalized economy, a job market that demands increasingly qualified workers, a technological boom, and occupational nomadism has made "education without borders" a reality. At the same time, it has turned foreign language teaching into a highly competitive market, one in which French has the significant advantage of being perceived as stripped of any imperialistic ambition. French is now seen as a language, perhaps the language, of culture and communication, not as a language of domination. The francophonia movement is becoming stronger, attracting new members, and organizing itself along federal lines. The Organisation Internationale de la Francophonie (OIF) receives some surprising membership applications, with the French-speaking population in some member states amounting to no more than 1%.

Motivations change with the changes in ways of life, the acceleration in communication, and the habit of international travel for work or tourism. Courses and activities need to meet the urgent and specific needs of people who travel more and more often, with less and less time at their disposal. Cultural activities—whether plastic arts, theater, dance, concerts, or festivals—are often conducted with the support of the French embassies and Culturesfrance, an offshoot organization from the Ministries of For-

Alliance Française Center in Ziguinchor, Senegal. © Alliance Française.

eign Affairs and Culture for the international promotion of the arts (www.culturesfrance.com). The flexible status of the Alliances, and the fact that they are locally based, are a great advantage in simplifying administrative procedures, bringing partners on board, and ensuring better project penetration among the local population.

For a long time the Alliances provided only paper documentary sources on France and French-speaking cultures. These were then expanded to include film archives, until they have now mushroomed into full-fledged multimedia centers. At the same time, culture is not confined to the theater, cinema, or dance. It also encompasses technology, research, and theory. If French is to remain a living language in the era of the global village, it must be a vehicle in which its users can portray their history and debate any issue of contemporary concern, whether ecology, bioethics, multiculturalism, conservation, or the relationships between religion and politics, and between public security and human rights. Over the years the Alliance has developed a kind of practical genius for international cooperation and a universal network of friends and supporters. As such, it is being increasingly invited to take up where the cultural activities of the embassies leave off, with an operational scope broadened to the entire field of cooperation.

Thus in Asmara, Eritrea, the Alliance subsidizes the publication of works on oral poetry and history; it also supports studies on the Nara and Dahalik languages, and offers grants for master's degrees at the Sorbonne. In Zimbabwe, despite the shortage of fuel, foreign currency, and staple foods, the Alliance organizes music-making workshops between French and local musicians. In Nairobi, it helped stage a Victor Hugo play in Swahili in the home of a French director, while in Ulan Bator the recently established Alliance hosted a symposium with the local Academy of Sciences on European archeology. It was the Alliance, which, with the Louvre and French National Library, brought restorers together from Ecuador, Bolivia, Peru, and Venezuela for a seminar on restoration in the graphic arts. In Kingston, Jamaica, the Alliance broadcasts Radio France 1 programs. In the Unites States, Alliances have hosted talks by the paleontologist Jean Clottes and the French Academician Hélène Carrère d'Encausse. Their Canadian counterparts have organized debates on Islam and multiculturalism. The Washington Alliance has presented a festival of films never shown in the United States, from Mauritania, Vietnam, Egypt, Morocco, France, and the Lebanon. The movement can claim a long litany of locally significant achievements.

A few figures

French across the world

- French is the mother tongue of 80 million people (the world's 11th largest language group). It is the second language of 100 million speakers.
- 250 million people are "occasional users of French."
- 82.5 million children and young adults are learning French or studying in French outside France (total teachers: 900 000).

The Alliance Française

- The Alliance is present in 134 countries on all 5 continents. In total there are 1074 Alliances and associated centers, 761 of which teach 450 000 students.
- The network comprises over 8000 voluntary administrators, and 11 000 staff, including 7 800 teachers. Receipts exceed 110 million euros, plus 3 million euros in local public funding, and another 3 million euros from private contributions. A total of 206 Alliances own their premises, while 182 are accommodated rent-free, generally by their local authority.

A new phase: the Alliance Française Foundation

In 1923 the celebrated grammarian André Thérive published a book entitled *"Le Français, Langue Morte [French, a Dead Language]."* He clearly wasn't a latter-day Nostradamus. Admittedly, once the country became reconciled to its loss of cultural and diplomatic preeminence, a couple of decades went by in which French sought to reposition itself. But perhaps now it is finding that position as the embodiment of a cultural and political alternative, a certain idea of quality of life, and a novel approach to the environment. Just as Latin did not displace Greek, which remained very much alive as a language of culture and trade in Greece and Asia Minor, so the French language, at the confluence of a variety of African, Asian, and American cultures, can, in the view of the Alliance Française, aim for a similar mediator role.

Be that as it may, it is important for the linguistic diversity battle to be joined, in particular by respected institutions—no more so than in Europe itself where the "maximin" principle threatens to become the norm for communication within the Union's institutions. This concept from practical linguistics entails the maximization of minimum competence, ie, when several people

with different languages need to communicate, the language they choose must be that best known by the member of the audience who knows it least. Under the maximin principle, in any political gathering comprising over 20 languages, convergence to a single one of them, English, appears inevitable.

Based on another linguistic concept, the Humboldt-Sapir-Whorf hypothesis, named after its main proponents, we have reason to believe that the structure of a language determines the way in which we see the world. In other words, sharing a language means sharing a view of the world. It is therefore important that ideas get an opportunity to be formulated in languages other than the dominant language, if we are to escape what George Orwell, in his preface to *Animal Farm,* called "the gramophone mind."

Alliance Française Center in Nairobi, Kenya. © Alliance Française.


Building housing the Alliance Française Center in Taibei, Taiwan. © Alliance Française.

In this sense the Alliance Française considers that its mission extends beyond simply expanding the influence of French language and culture. It involves what the literary historian Marc Fumaroli (1932-) has defined as the French art of "untying tongues and thawing hearts." Its banner is the "diversity" esthetic that Victor Segalen (1878-1919), physician, poet, and sinologist, celebrated as essential to our development.

Once it had launched the international movement in 1883, the Paris Alliance was essentially a provider of moral support, in the absence of sufficient resources of its own. However, in a world harboring fresh communicational and organizational challenges, the Paris Alliance is facing increasing demands to improve the coordination and development of the network it spawned, upgrade the services on offer, enhance local staff training, and support individual Alliances in their cultural undertakings and equipment requirements. It was therefore decided to establish an international foundation to provide individual Alliances with the requisite intellectual, moral, and technical support for continuing their work. An additional remit of this foundation, which comprises experts in association management and operational development alongside training and cultural affairs consultants, is to map out the broad directions to be taken by the Alliance movement and to reflect the ambitions shared within this vast collective enterprise.

Such then is the portrait of the Alliance Française as it seeks to embody, under contemporary guise and with renewed impetus, the grandiose ambitions expressed by its bearded and behatted founding fathers one 19th century July afternoon in a little room on the boulevard Saint-Germain. ❒

L'Alliance Française : petite histoire d'une grande institution

En juillet 1883 naît à Paris l'Alliance Française, « association nationale pour la propagation de la langue française dans les colonies et à l'étranger », *mouvement culturel qui connaîtra une brillante carrière à travers un XX^e^ siècle où faillit sombrer l'humanisme, et qui aborde le XXI^e^ en pleine prospérité, avec de nouveaux projets. Le mouvement repose sur trois principes d'une surprenante modernité. Le premier consistait à l'époque à tenter de restaurer le prestige de la France, entamé par la défaite de 1870, en empruntant les voies pacifiques de la langue et de la culture. Le rayonnement culturel plutôt que la guerre, en somme. Le second principe, assez peu dans la tradition française, est de miser sur une association non étatique pour mettre en œuvre une politique d'influence internationale. Le troisième est de confier le rayonnement culturel et linguistique de la France à des étrangers. En effet, les Alliances à travers le monde sont de droit local, dirigées bénévolement par des nationaux qui ont l'amour de la culture française. La formule connaîtra un succès extraordinaire. Du Canada à la Terre de Feu, de l'Afrique du Sud aux limites du cercle polaire, de la Russie à l'Inde, en Chine comme en Océanie, plus d'un millier d'associations accueillent aujourd'hui plus de 450 000 étudiants, et plus de 6 millions de personnes aux manifestations culturelles qu'elles organisent. Une Fondation est créée en 2007 pour à la fois assurer l'avenir de cette entreprise exceptionnelle et contribuer à la promotion de la diversité culturelle dans le monde.*

Medicographia
A Servier publication

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◆ **All texts should be submitted in English.** In the case of translations, the text in the original language should be included.

◆ Provide black and white **photograph(s) of author(s).**

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2. Darling RC, Brewster DC, Ottinger LW. Autopsy study of unoperated abdominal aortic aneurysms: the case for early resection. *Circulation.* 1977;56(suppl II):II161-II164.
3. Schulman JL. Immunology of influenza. In: Kilbourne ED, Alfade RT, eds. *The Influenza Viruses and Influenza.* Orlando, Fla: Academic Press Inc; 1975:373-393.

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